PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION

Dissertation submitted to

The Tamilnadu Dr. M.G.R Medical University

In partial fulfillment of the regulations for the award of the degree of

M.D. BIOCHEMISTRY - BRANCH XIII

DEPARTMENT OF BIOCHEMISTRY

GOVERNMENT MOHAN KUMARAMANGALAM MEDICAL COLLEGE

SALEM – 636 030

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI – 600 032

TAMILNADU

MAY 2019

BONAFIDE CERTIFICATE

This is to certify that this dissertation work entitled **"PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION"** is the original bonafide work done by **DR. M. MOHAMED ALI**, Post Graduate Student, Department of Biochemistry, Government Mohan Kumaramangalam Medical College, Salem under our direct supervision and guidance.

Dr. M.K. RAJENDRAN M.S., M.Ch.,
Dean
Government Mohan Kumaramangalam
Medical College and Hospital,
Salem.

Prof. Dr. R. RANGARAJAN MD.,
Professor & HOD,
Department of Biochemistry,
Government Mohan Kumaramangalam
Medical College,
Salem.

CERTFICATE BY THE DISSERTATION GUIDE

This is to certify that this dissertation entitled as, **"PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION"** is a bonafide work done by **Dr. M. MOHAMED ALI**, Post Graduate Student, Department of Biochemistry, Government Mohan Kumaramangalam Medical College, Salem, under my supervision and guidance, in partial fulfillment of the university rules and regulations for the award of **MD DEGREE** in **BIOCHEMISTRY BRANCH-XIII,** during the academic period from December 2017 to June 2018.

Dr. A.LEENADEVI, MD.,
Associate Professor,
Department of Biochemistry,
Government Mohan Kumaramangalam
Medical College,
Salem – 636 030.

DECLARATION

I, **Dr.M.MOHAMED ALI**, Post Garaduate, Department of Biochemistry, Government Mohan Kumaramangalam Medical College, solemnly declare that the dissertation titled , “PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION” is the bonafide work done by me at Department of Biochemistry, Government Mohan Kumaramangalam Medical College under the expert guidance and supervision of **Dr. A. LEENADEVI, M.D.,** Associate Professor, Department of Biochemistry, Government Mohan Kumaramangalam Medical College. The dissertation is submitted to the TamilNadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch XIII) in Biochemistry.

Place : Salem

Date : **Dr. M.MOHAMED ALI**

SPECIAL ACKNOWLEDGEMENT

The author gratefully acknowledges and sincerely thanks Professor **Dr. M.K. RAJENDRAN M.S., MCh.,** Dean, Government Mohan Kumaramangalam Medical College and Hospital, Salem, for granting his permission to utilize the facilities of this Institution for the study.

ACKNOWLEDGEMENT

The author expresses his warmest respects and profound gratitude to **Dr. R.RANGARAJAN M.D**., Professor & HOD, Department of Biochemistry, Government Mohan Kumaramangalam Medical College, Salem, for his academic enthusiasm and for facilitating this research work in the institute.

The author also expresses his heartfelt gratitude to **Dr. A.LEENADEVI M.D.,** for her intellectual and valuable guidance, unfailing support, encouragement and continuous inspiration throughout the period of her study.

The author is extremely thankful to **Dr. KANNAN M.D., DM (CARDIOLOGY)** Professor & HOD, Department of Cardiology, Government Mohan Kumaramangalam Medical College Hospital, Salem, for granting permission to obtain blood samples from the patients.

The author expresses his thanks to **Dr. S.SENTHILKUMARI M.D.,** the **Associate Professor,** Department of Biochemistry, Government Mohan Kumaramangalam Medical College, for her encouragement, insightful comments and suggestions.

The author expresses his warm respects and sincere thanks to **Assistant Professors, Dr. B. Shameem, Dr. U.N. Priyadharshini, Dr. S. Anandhi, Dr. G. Poongodi, Dr. N. Vijayabanu, Dr. P. Sangeetha, Dr. K.Kughapriya, Dr. Sathya, Dr. Ravisekar,** Department of Biochemistry, Government Mohan Kumaramangalam Medical College, for their valuable suggestions regarding the practical issues of research which is something beyond the textbooks.

The author expresses warm respects to the members of the Institutional Ethical committee for approving the study.

The author expresses his special thanks to Lab technicians for their timely help and cooperation during sample collection.

The author is indebted to the patients from whom blood samples were collected for conducting the study.

The author expresses his thanks to all the colleagues in the department, for their constant encouragement throughout the study period.

The author gratefully acknowledges the help rendered by his co Postgraduates **Dr. R .Kalaiselvi and Dr. P.M. Sasikala** for the statistical analysis of the study.

The author expresses his special thanks to his wife **Mrs. Noorjahan,** his daughters **Fathima sana mohideen, Salaama marjan** and his family members for the moral support and encouragement extended by them which gave fulfillment to the dissertation work.

Above all, the author is grateful to the Almighty for providing this opportunity, without whose grace nothing could be accomplished.

[Urkund] 7% similarity - doctormohmadali@gmail.com

Inbox ×

report@analysis.urkund.com

Oct 29, 2018, 5:38 PM (4 days ago)

to me

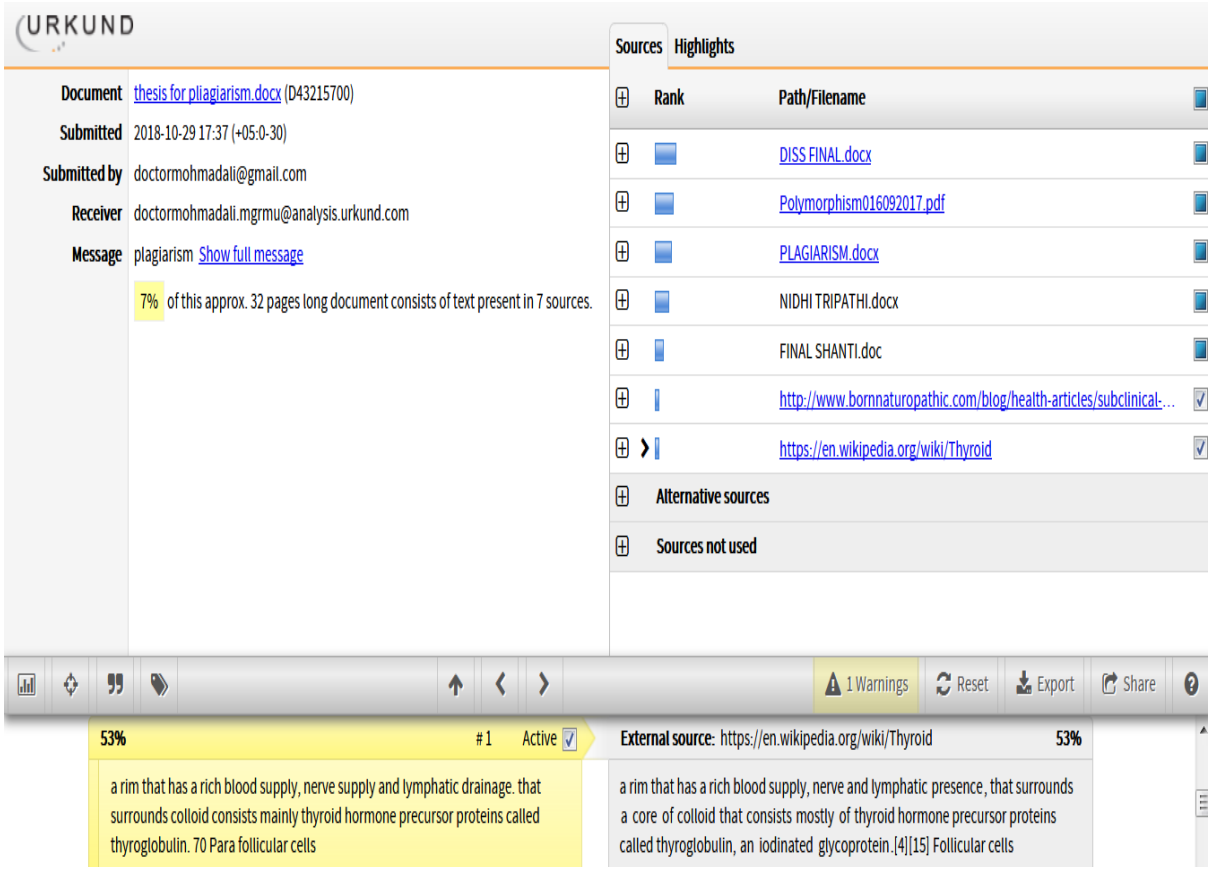
Document sent by: doctormohmadali@gmail.com
Document received: 10/29/2018 1:06:00 PM
Report generated 10/29/2018 1:08:24 PM by Urkund's system for automatic control.

Student message:

Document : thesis for pliagiarism.docx [D43215700]

IMPORTANT! The analysis contains 1 warning(s).

About 7% of this document consists of text similar to text found in 140 sources. The largest marking is 52 words long and is 90% similar to its primary source.


URKUND
Document thesis for pliagiarism.docx (D43215700)
Submitted 2018-10-29 17:37 (+05:0-30)
Submitted by doctormohmadali@gmail.com
Receiver doctormohmadali.mgrmu@analysis.urkund.com
Message plagiarism Show full message
7% of this approx. 32 pages long document consists of text present in 7 sources.
Sources Highlights
Rank Path/Filename
DISS FINAL.docx
Polymorphism016092017.pdf
PLAGIARISM.docx
NIDHI TRIPATHI.docx
FINAL SHANTI.doc
http://www.bornnaturopathic.com/blog/health-articles/subclinical-...
https://en.wikipedia.org/wiki/Thyroid
Alternative sources
Sources not used
1 Warnings
Reset
Export
Share
53% #1 Active
a rim that has a rich blood supply, nerve supply and lymphatic drainage. that surrounds colloid consists mainly thyroid hormone precursor proteins called thyroglobulin. 70 Para follicular cells
External source: https://en.wikipedia.org/wiki/Thyroid 53%
a rim that has a rich blood supply, nerve and lymphatic presence, that surrounds a core of colloid that consists mostly of thyroid hormone precursor proteins called thyroglobulin, an iodinated glycoprotein.[4][15] Follicular cells

CERTIFICATE

This is to certify that this dissertation work titled **"PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION"** was done by the candidate **Dr.M.MOHAMED ALI** with the Registration Number **201623602** for the award of **MD DEGREE** in the branch of **BIOCHEMISTRY (BRANCH – XIII).** I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **7 percentage** of plagiarism in the dissertation.

Guide and Supervisor Sign with Seal

PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION

ABBREVIATIONS

ACS	Acute Coronary Syndrome
AGEP	Advanced Glycation End Products
Cal-LDL-C	Calculated Low Density Lipoprotein-Cholesterol
CHD	Coronary Heart Diseases
CK-MB	Creatine Kinase - Muscle Kidney Fraction
CRP	C Reactive Protein
CVD	Cardio Vascular Diseases
DI	Deiodinase
DUOX	Dual Oxidase
ESS	Euthyroid Sick Syndrome
ET-1	Endothelin -1
FT_3	Free Triiodothyronine
FT_4	Free Thyroxin
HDL-C	High Density Lipoprotein cholesterol
IHD	Ischemic Heart Diseases
LDL-C	Low Density Lipoprotein-Cholesterol
MI	Myocardial Infarction
NO	Nitrous Oxide
NSTEMI	Non ST elevation Myocardial Infarction
ROS	Reactive Oxygen species
SCH	Sub Clinical Hypothyroidism
STEMI	ST elevation myocardial infarction
TRH	Thyrotophin releasing hormone

CONTENTS

INTRODUCTION

Coronary artery heart disease is a global health problem and also an important cause of death in all age groups.[1] Studies are being done in both developed and developing countries to find its risk factors. The results of various studies have revealed atherosclerosis of the coronary vessels due to altered lipid profile is the commonest mechanism in most of the patients. In many patients the risk factors are identified only when they succumbed to life threatening events like acute coronary syndrome.

Screening for diabetes and hypertension identifies pre diabetic and pre hypertensive states. Prevention of the emergence of these risk factors constitutes the primordial prevention. In the same way, the overt hypothyroidism has its subclinical counterpart which is also being proposed as a risk factor for coronary artery heart disease.

Subclinical hypothyroidism is a common problem and occurs in 3% to 8% of the population and 2-5% of SCH carries a risk of progression to overt hypothyroidism in every year.[2,3] Many prospective studies have given varied results regarding its association with altered lipid profile. There is a significant association between subclinical hypothyroidism and increased risk of coronary artery heart disease, cardiac failure and death with higher TSH levels, particularly in those patients with TSH levels ≥ 10.0 m IU/L.[4]

In this study thyroid function tests and lipid profile were done in ACS patients to know the prevalence of the subclinical hypothyroidism and the association between them as an attempt to identify the emergence of hypothyroidism as a risk factor for acute coronary syndrome.

REVIEW OF LITERATURE

EPIDEMIOLOGY

Global burden of Coronary Heart Diseases

In the U.S., Coronary Heart Disease is the leading cause of mortality in adult population accounting for nearly one third of all deaths in the persons over the age of 35 years.[5] According to 2016 Heart Disease and Stroke Statistics update of the AHA report, overall death rate from CHD was 102.6 per 100,000.[6] Patients were asymptomatic for a prolonged period in spite of the evidence of CHD with the progression of atherosclerosis over many years. Non-obstructive CHD patients when comparing with patients without the evidence of CHD had worst prognosis even though they are asymptomatic.[7, 8]

Only a few population-based studies have shown recent trends in the incidence of MI. In many time periods (1971–1982, 1982–1992, [9] 1975–1997, [10] 1994–1999, [11] and 1987–2006) observational studies were done. They have found no reduction in the incidence of MI.[12] After 2000 AD, the advent of the more sensitive troponin assays (comparing with CK-MB) helped to diagnose MI even though the area of infarct was small. This could have potentially masked the actual reduction in MI incidence during these time periods.[13]

Several studies have been done to know the influence of sex and race on the incidence of MI. The Atherosclerosis Risk in Communities (ARIC) study concentrated on the risk of CHD events in 360,000 residents aged 35–74 years in four communities:

Forsythe County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland.[14, 15]

This study was done during the period between 1987 and 1996. A definite or probable MI was diagnosed in 14,942 hospitalized patients. The age-adjusted incidence of hospitalized MI was highest in black men and lowest among white women.

The age-adjusted incidence of first episode of MI was relatively stable during 1987–1996 in males and females for white people. Also, there was a non-significant trend to increase by1.1% in men and 1.7%in women per year.

In black people there was a significant increase in the trend (4.1% in men and 3.9% in women per year). The study also showed a reduction in the incidence in recurrent MI in both genders (−1.9% in men and −2.1% in women per year). Post- MI mortality rate had decreased significantly during the period between 1987–1996 (by −6.1% in men and −6.2% in women). Although coronary atherosclerosis and ACS have male preponderance, as a result of dietary habits, smoking and mental stress the incidence of it is increasing in women.

ACS trends in India

Mortality at early age was noted in many studies of migrant Indians in the 1980s. It was the INTERHEART study (a large international case-control study across 52 nations) that confirmed the early age of onset of incident myocardial infarction among patients from South Asia.[16] In this study, the median age of MI

in South Asians was 52 years in comparison with 62 years in the European origin cohort. This study found that the equal presence of usual cardiovascular risk factors of elderly persons in the young South Asians and occurrence of early onset of myocardial infarction.

According to the Global Burden of Disease study (2010), 24.8% of all deaths in India were attributable to Cardio Vascular Diseases.[17] The age-standardized CVD mortality rate of 272 per 100000 population in India was found to be higher than the global average of 235 per 100000 population.[17] Ischemic heart disease (IHD) and stroke had been the important causes for the majority of deaths due to cardio vascular diseases in India (83%). IHD had predominance over all other causes. The years of life lost attributable to CVD in India had increased by 59% from 1990 to 2010 (23.2 million to 37 million).[17]

Risk factors burden in India

In 2013, the International Diabetes Federation found an estimate of diabetics as 65.1 million in India and most of them were adults of working age.[17] It has been estimated that the number of diabetics will increase to 101 million by 2030.[17]

In the urban population of India, the prevalence of diabetes mellitus has nearly doubled in the past 20 years, from 9% to 17% and in rural population it has increased to almost four times, from 2% to 9% .[17]

Recently, it has been estimated that 275 million persons aged ≥15 years consume tobacco in India.[18] The deaths associated with tobacco in India are high. It is estimated that 1 million deaths are caused by it annually.[19]

The prevalence of hypertension in adult Indians is found to be 30% (34% in urban areas and 28% in rural areas).[20] The number of hypertensive persons is expected to double from 118 million in 2000 to 213.5 million by 2025.[21]

National Sample Survey Organization surveys showed that, from 1972 to 2000, fat intake of Indians increased from 24 to 36 g/day in rural population; and from 36 to 50 g/day in urban population. [22]

In the ICMR-INDIAB study, at least 1 altered lipid fraction was found in majority of the people. Only 20% had their lipid profile (total cholesterol, triglycerides, LDL-C and HDL-C) within the normal range.[23]

Diagnosis of Acute Coronary Syndrome

The **Acute Coronary Syndrome** (ACS) is a broad term refers to any group of clinical symptoms that occurs due to acute myocardial ischemia and covers the following clinical conditions:

- Unstable angina (UA),
- Non ST-segment elevation myocardial infarction (NSTEMI) and
- ST-segment elevation myocardial infarction (STEMI)

Unstable angina (UA) and NSTEMI

Cause:

Partial or intermittent occlusion of coronary artery

The clinical presentation

(1) Chest pain at rest (usually lasting >20 minutes)

(2) New-onset of severe chest pain (within two months) and

(3) Chest pain that increases in intensity, duration, frequency, or any combination of these factors.

Both NSTEMI and unstable angina have similar pathophysiologic origins and clinical presentations but their clinical severity differ.

NSTEMI is diagnosed when the ischemia is sufficiently severe enough to damage myocardium resulting in the release of cardiac biomarkers into the circulation. (Cardiac specific troponins T/I or Creatine Kinase - MB). The patient is diagnosed as a case of UA if cardiac bio markers are not released in blood. The differential diagnosis of UA, NSTEMI and STEMI is shown in Fig 1.

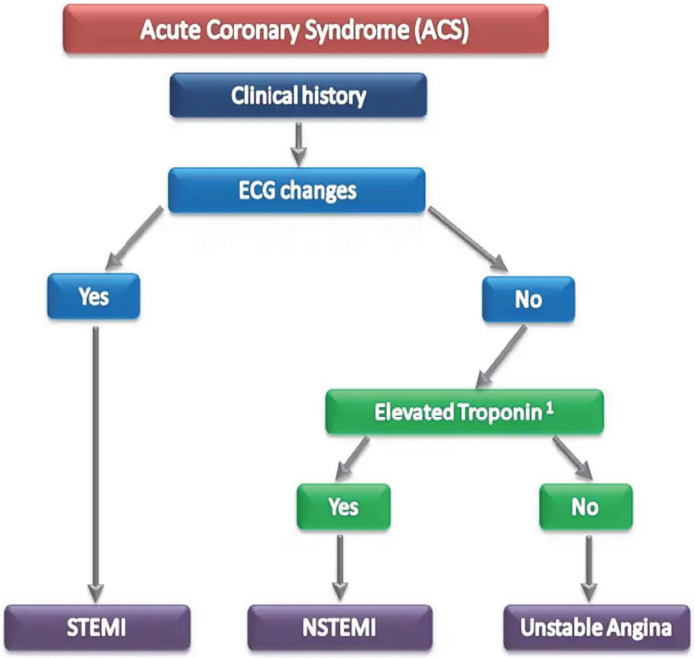


Figure1. Diagnosis of STEMI,NSTEMI and UA

STEMI

Cause:

Complete occlusion of coronary arteries.

Signs and Symptoms

- Chest pain with or without radiation to arm, neck, back, or upper abdomen
- Shortness of breath, diaphoresis, nausea, light headedness, tachycardia, tachypnea, hypotension or hypertension, decreased arterial oxygen saturation (SaO2) and rhythm abnormalities
- Pain at rest or with exertion; causing limitation of activity

DIAGNOSTIC FINDINGS

Electrocardiography

- ST-segment depression and /or T-wave inversion on ECG - NSTEMI and UA
- ST segment elevation - STEMI

Cardiac biomarkers

According to European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation (WHF) the elevation of cardiac enzymes only states that myocardium has been injured. It will not point out the underlying mechanism which is responsible for the injury.

Troponins:

According to the revised criteria of WHO (in 2000) a cardiac troponin rise accompanied either by typical symptoms, pathological Q waves, ST elevation or depression or coronary intervention is diagnostic of ACS.

They are regulatory proteins seen in both cardiac and skeletal muscles. There are three sub units: Tn I, Tn T and Tn C. Since distinction exists between them in the sub forms of Tn I and TnT, immuno assays have been developed to differentiate their origin whether from skeletal muscle or cardiac muscle.

Reference ranges for Troponin assay

1. Upper percentile reference limit
2. Coefficient of variation

To overcome problems of imprecision seen in TnI assays at 99th percentile it is recommended to raise the CV a little higher. To overcome the disadvantages of these assays high sensitive or ultrasensitive troponin assays are recommended by investigators.[24] Point of care assays for CK-MB, myoglobin and Troponins (Tn I and Tn T) are available.

- **The advantage of Troponins over other cardiac markers.**

  Elevated Troponin levels can be utilized to predict adverse cardiac events and cardiac mortality

Creatine Kinase–MB:

Before the advent of cardiac troponins, CK-MB isoenzyme was the choice for the diagnosis of acute myocardial infarction.

It appears 4-6 hours after the onset of the symptoms, with the peak at 24 hours and comes back to normal in 48 to 72 hours

Two consecutive elevations above the upper normal level or single value twice the upper limit of normal were used as diagnostic criteria.

Disadvantage of CK-MB:

1. False positive results can occur in severe trauma or myopathy.

   To improve the specificity, CK-MB/total CK relative index can be used.[25]

   - A ratio more than 5 indicates cardiac origin for elevation.

- A ratio less than 3 indicates the source from skeletal muscle.
- Between 3-5 is not possible to make a definitive diagnosis.

Two isoforms occurs for CK-MB iso enzyme, CK -MB1 and CK-MB2.

- Normally CK-MB1 level predominates in serum. CK-MB2/CK-MB1 ratio of 1.7 is considered as a positive result.

2. According to a report from the multicenter GRACE registry, stating the clinical course of more than 10,000 patients with ACS,

The death rate at hospital was highest when both troponin and CK-MB were positive. The mortality rate was intermediate in troponin-positive/ CK-MB-negative patients, and lowest death rate was noted in patients in whom both markers were negative and in those who were troponin-negative/ CK-MB-positive.

So, isolated CK-MB elevation has limited prognostic value in patients with a non-ST elevation ACS.

Myoglobin:

It rises 2-4 hours after the onset of myocardial infarction, gets peak level at 6-12 hours and returns to normal within 24-36 hours. It lacks cardiac specificity. If serial myoglobin assay is done every 1-2 hours a rise of 25 - 40% is a firm indication for myocardial infarction.

Newer cardiac biomarkers:

They are useful to indicate prognosis and predict of adverse cardiac events.[26]

1. B-type natriuretic peptide

In multiple studies, the mortality of CHD patients was found to be doubled when both Tn I and BNP were increased.

2. C-Reactive protein

Nonspecific nature limits its use. Along with Tn I and BNP it is useful to predict the prognosis of ACS.

3. Myeloperoxidase

4. Ischemia modified albumin

This fraction of albumin is produced when circulating albumin gets contact with ischemic areas of heart. IMA levels increase within minutes of transient ischemia, reaches peak within 6 hours, and can remain elevated for as long as 12 hours. It can be measured by albumin cobalt binding assay.

Disadvantage:

False positive results occurs in

- Cirrhosis of liver
- Active infection
- Malignancy

ATHEROSCLEROSIS AND ACUTE CORONARY SYNDROME

CORONARY CIRCULATION

Vascular system which supplies blood to heart is called coronary circulation. Two main coronary arteries (right and left) arise from root of thoracic aorta. The right coronary artery supplies mainly the right side of the heart. The left coronary artery gives the left anterior descending artery and the circumflex artery branches which supply the left side of the heart. Occlusion of the left anterior descending artery is often called as widow maker infarction which causes high death rate. Major blood supply of heart is shown in Figure 2.

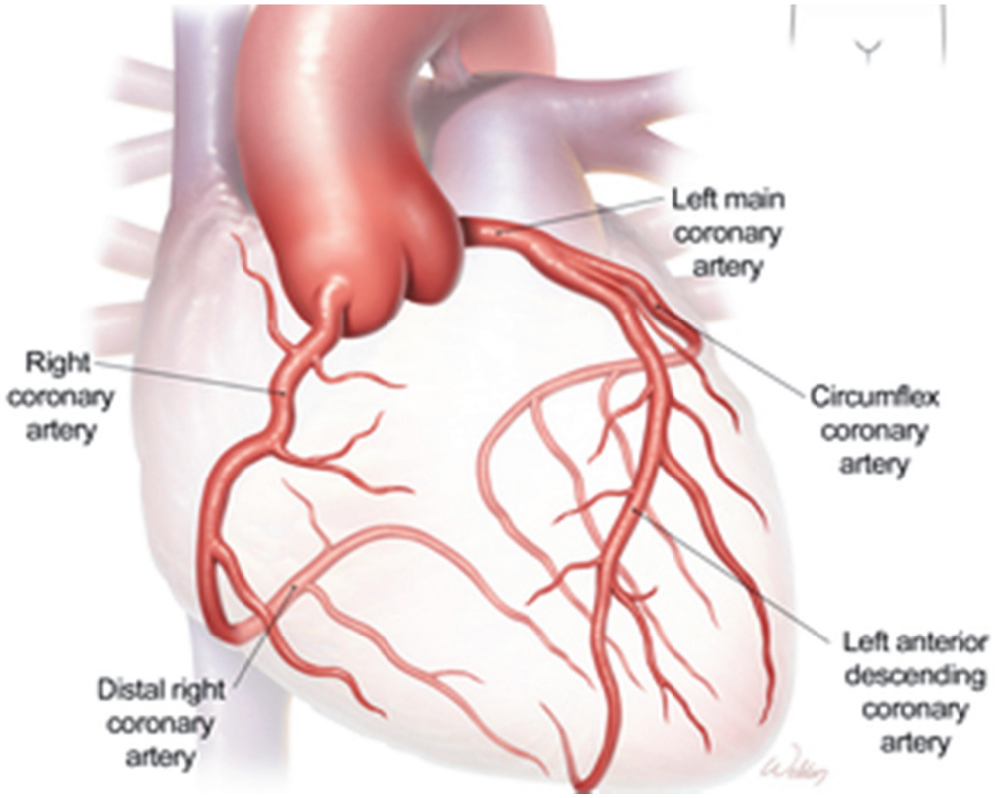


Figure2. Blood supply of the heart

ATHEROSCLEROSIS

Definition

The name Atherosclerosis is derived from the Greek words 'sclerosis' meaning hardening and 'athere' meaning gruel (accumulation of lipid). The process is characterized by deposition of cholesterol, infiltration by macrophages, proliferation of smooth muscle cells (SMC), accumulation of connective tissue components and thrombus formation.

Atherosclerosis is no longer a pathological process caused solely by the increased lipid content of the body. By new insight it is found to be a multifactorial disease. Damage of vascular endothelium and generation of reactive oxygen species and other free radicals have been recognized as factors almost in all the pathways leading to the development of atherosclerosis due to dyslipidemia, diabetes mellitus, hypertension or smoking.

Hyperhomocysteinemia, C-reactive protein, infections like chlamydia and auto immune disease like systemic lupus erythematosus have arisen as new risk factors.

Now, **Atherosclerosis can be defined as a chronic inflammatory process with an autoimmune component.** Genes related to atherosclerosis and genetic basis of atherogenesis have been known. So, in future gene therapy will become a promising mode of management of atherosclerosis. Table.1 shows risk factors of CHD and Figure 3.shows common risk factors and their mechanisms.

Table-1. RISK FACTORS OF CARDIO VASCULAR DISEASE

Class 1. Modifiable	Class 2. Modifiable	Non- modifiable
Smoking Elevated total cholesterol Elevated LDL-cholesterol Low HDL-cholesterol Excess fat/cholesterol diet Left ventricular hypertrophy Thrombogenic factors	Lipoprotein (a) Diabetes mellitus Hypertension. Physical inactivity Obesity High triglycerides High homocyseine Increased hs-CRP Stress.	Age Male gender Family history of premature CHD

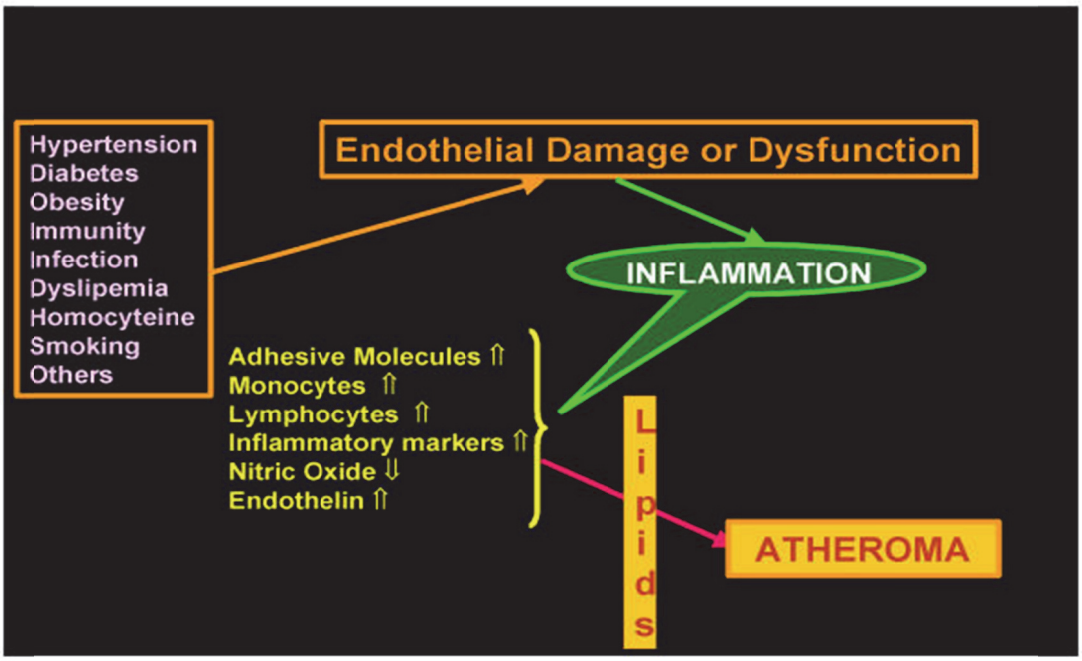


Figure. 3 Risk factors of atherosclerosis and their mechanisms

LIPID METABOLISM AND ITS ROLE IN ATHEROSCLEROSIS

Triglycerides

Reduced blood levels of high density lipoprotein (HDL) and hypertriglyceridemia have been shown to be responsible for the genesis of atherosclerotic lesions.[27]According to the National Cholesterol Education Program guidelines patients having less than 1 mmol/L of HDL will have the risk for developing coronary vascular disease. The Collaborative Heart Disease Study done in the United Kingdom done in two places states that serum triglyceride levels were of more predictive value than total cholesterol for the determination of the risk for coronary vascular disease. [28] These studies reported that triglyceride levels more than 2.25 mmol/L and LDL: HDL ratios more than 5 were associated with a fivefold increase in the risk for cardiovascular morbidity, particularly in persons with a metabolic syndrome. Serum triglyceride level of 1.7 mmol / L is considered as the upper normal limit.

Clinical significance

Triglyceride concentrations are usually elevated in both type 1 and type 2 diabetes mellitus and considered as a risk factor for coronary artery heart disease. Excess insulin causes non enzymatic glycation of the lipoproteins, which interact with cytokines and growth factors, and has an important role in atherogenesis. [29]

High Density Lipoprotein-Cholesterol

HDL plays vital role in the development of atherosclerosis due to its function in reverse cholesterol transport. Cell surface HDL receptors mediate the protective effects of HDL which have opened new ways for the management of atherosclerotic cardiovascular diseases. SR-B1, a HDL surface receptor mediates selective HDL cholesterol uptake. The pro atherogenic activity of LDL is also counteracted HDL by mobilizing cholesterol from intimal layer of arterial wall and transporting it to the liver for excretion into the bile. Studies have found that HDL may accept, transport and inactivate oxidized LDL (oxLDL).

Clinical significance

Evidences from experimental studies have given suggestion that SR-BI gene transfer can modify the course of the atherogenic cascade by elevating the plasma HDL. Mechanisms of HDL not related to lipid metabolism are:

(a) HDL inhibits adhesion and migration of monocytes into the arterial intima

(b) Stimulates cell repair and proliferation

(c) Preserves endothelium-dependent vascular activity

(d) Inhibits growth factor induced VSMC proliferation and

(e) Prevents thrombosis. [30]

Role of CETP in atherosclerosis

It is a hydrophobic glycoprotein with Molecular Weight of about 70,000 to 74,000 Da. It is synthesized in many organs of the body apart from the heart and induced during the differentiation of monocytes into macrophages. It is a major protein involved in reverse cholesterol transport. It regulates the plasma concentrations of HDL cholesterol and the size of HDL particles.

Clinical significance

Persons having deficiency of cholesterol ester transfer protein are known to have marked hyper alphalipoproteinemia.[31]

Enzymes of lipid metabolism

Lipoprotein lipase and hepatic lipase are the two important enzymes involved in lipoprotein metabolism. They belong to the family of neutral lipases. These two lipases play important role in the metabolism of triglyceride-rich proteins.

Lipoprotein lipase is intravascular in location and attached to endothelial cells. This enzyme is produced chiefly in cardiac and skeletal muscles. These organs utilize preferably fatty acids of adipose tissue and mammary glands to meet their energy requirement. Lipoprotein lipase hydrolyses lipid fractions on chylomicrons and very low density lipoprotein (VLDL) and converts them into smaller remnants so that they can be quickly cleared from the circulation.

Hepatic lipase is produced and released by hepatocytes and affects HDL metabolism. Accumulation of β-VLDL observed in hepatic lipase deficient people points that triglyceride-rich particles could be a substrate for this enzyme. Studies on hepatic lipase enzyme revealed that it is essential for LDL synthesis and its redistribution into HDL fraction. [32]

Defects in these proteins have pathological implication in pathogenesis of atheroma. (Lipoprotein lipase produced by macrophages is important in plaque formation). Changes in hepatic lipase activity produced by treatment alter the density of LDL. This influences coronary artery disease progression and produces a favorable outcome. [33]

Positive correlation exists between post prandial lipemia and the progression of coronary artery disease since increased blood level of triacylglycerol is achieved from dietary sources. High level of chylomicrons and small dense LDL particles with reduced HDL levels occurs after a fatty meal. This biochemical profile promotes thrombosis by activating coagulation factor VII and platelet activator inhibitor. [34]

LDL-Cholesterol

Sequestration of LDL particles in the vessel wall and its subsequent oxidation is considered to be an important event in the early stages of an atherosclerotic lesion.

1. OxLDL particles enhance the recruitment and retention of monocytes and lymphocytes
2. They promote conversion of monocytes into macrophages
3. Increase the production of various growth factors and cytokines.

The toxic effect of oxLDL has been demonstrated in cultured Vascular Smooth Muscle Cells and fibroblasts. Animal studies show that oxLDL induces the release of FGF-1 in a concentration-dependent manner. This effect has good correlation with the extent of oxidative modification of oxLDL. [35] During the oxidative process of LDL particles, the Apo lipoproteins, cholesterol and the esterified unsaturated fatty acids in phospholipids or cholesterol esters are modified.

LDL MODIFICATION AND OXIDATION

15-LIPO OXYGENASE

In reticulocytes of mammals, eosinophils and certain other cell types, 15-LOX are expressed at high concentrations. But they are not expressed in peripheral monocytes or normal vessel wall. However, the expression of 15-LOX can be induced in human monocytes in the presence of interleukin IL-4&IL-13. Studies with transgenic mice with a knockout for the LOX gene have shown a reduction in the incidence of atherosclerosis. In vitro, LOX modifies LDL in such a way that it can be taken up by macrophages.

So, overexpression of 15-LOX in macrophages and monocytes increases capability to metabolize LDL particles to counter the deleterious effects of hypercholesterolemia. The available data suggest that overexpression of 15-LOX is to afford protection against atherosclerosis. Accordingly, it has been concluded that 15-LOX is a complex enzyme with proatherogenic and antiatherogenic effects.[36] LDL is formed in the early stages of atherosclerosis, while oxLDL is formed in the later stages.[37] Although LDL binds to LDL receptor and oxLDL binds to scavenger receptor, the vascular effects of minimally modified LDL and oxLDL are similar. Both of them

1. Activate endothelial cells, SMC and monocytes.
2. Facilitate vasoconstriction, thrombosis and platelet aggregation associated with the activation of intracellular protein kinases and transcription factors such as NFκB or activator protein-1.
3. Causes expression of cellular adhesion molecules on endothelial cells and monocytes and the synthesis of monocyte chemo attractant protein-1 (MCP-1), cytokines and growth factors particularly platelet-derived growth factor (PDGF) and procoagulant factors such as plasminogen activator inhibitor-I .
4. Induces a vasoconstrictor state by reducing the formation of the endothelium-derived vasodilators, NO and prostaglandin while enhancing the production of the vasoconstrictor endothelin-1 (ET-1).

In the sub endothelial space, the uptake of oxLDL by monocyte-derived macrophages reduces macrophage migration and leads to the formation of foam cells, the hallmark of atherosclerotic lesions. OxLDL is chemotactic for monocytes and T-cells. Furthermore, monocytes or macrophages present antigenic epitopes of oxLDL to B-cells, inducing the formation of antibodies to oxLDL and an immune reaction towards deposited oxLDL.[37] Endothelial cells mediate the uptake of oxLDL by a recently cloned lectin-like oxLDL receptor-1, which is also involved in mediating endothelial phagocytosis of aged and apoptotic cells. The production of lectin-like oxLDL receptor-1 in endothelial cells is induced by tissue necrosis factor-alpha (TNF-α), ET-1, shear stress, tissue growth factor-beta (TGF-β) and angiotensin II, which accelerates foam cell formation by increased uptake in endothelial cells and macrophages .[38]

Lipid peroxidation by ROS

In vivo and in vitro oxidative decomposition of omega-3 and omega-6 polyunsaturated fatty acids of membrane phospholipids by ROS results in lipid peroxidation. Beta-cleavage reaction of lipid hydro peroxides leads to the formation of aldehydic end products including malonyl dialdehyde, 4-hydroxy-2,3-nonenal and other 4-hydroxy-2,3 alkenals. These lipid metabolites are proposed as putative and ultimate toxic messengers. They are potential mediators of oxidative stress injury at a molecular level. These metabolites have been demonstrated in the sub endothelial space of human aortas. [35] Conversion of

polyenoic fatty acids to hydroperoxy derivatives by lipid peroxidizing enzymes is significant step in atheroma formation.

ROLES OF ENDOTHELIUM

Vascular endothelium is located between the blood and the vessel wall and functions as an endocrine organ. [39, 40] It plays key role in atherosclerosis.

Functions of endothelium

1. It regulates vascular tone, forms NO, Prostacyclins and Endothelins (ETs.)
2. It also maintains the composition of sub endothelial matrix.
3. It has an important role in proliferation of SMC, coagulation, fibrinolysis, permeability of lipoproteins and plasma proteins, and adhesion and migration of blood cells.

Causes of endothelial injury and dysfunction

1. Turbulent flow of the blood and stretching of the blood vessels causes stress and predispose the endothelium to early development of atherosclerosis. [41,42,43]
2. Most of damages to the endothelium are due to ROS produced by many risk factors such as cigarette smoking, stress, anaerobic metabolism and radiation.
3. Advanced Glycation End Products (AGEP) triggers oxidative stress through generation of ROS in diabetes mellitus and chronic uremia.[44] The AGEP peptides activates inflammatory cytokines and enhances Apo

lipoprotein B modification, which leads to increased uptake of LDL through the macrophage scavenger receptor (MSR) pathway.

Damaged or excessively activated endothelial cells secrete ET-1and factors affecting the differentiation and growth of VSMC. These exert a chemotactic action on leukocytes and platelets, and induce the expression of specific surface adhesion molecules (selectins, integrins and the supergene family of immunoglobulins) that interact with ligands on the surface of leukocytes and platelets.

Functions of ET-1

- It is a Vasoconstrictor
- Has mitogenic activity on SMC

Both mechanisms results in the synthesis and release of free radicals and inflammatory cytokines into the circulation. [45] At the sites of injury or inflammation, pro inflammatory cytokines such as IL-1 and TNF-α promote leukocyte adhesion and activation. They also generate activators of neutrophils, such as granulocyte macrophage colony stimulating factor, plasminogen-activating factor and IL-8.

Role of Nitrous Oxide

Current studies support two pathways for the endothelial isoform of NOS (eNOS) in atherogenesis.[46] Under normal conditions tetra hydro biopterin, an antiatherogenic molecule in tissue, regulates eNOS activity to activate NO production. However, in hypertension, hypercholesterolemia, smoking, and

diabetes mellitus increased oxidative stress oxidizes BH4, leading to BH4 deficiency. Lower BH4 levels in tissue induces the uncoupling of NOS and superoxide, causing endothelial-cell damage.[47]

Other proteins involved in ROS production and atherogenesis are Chymase, Angiotensin II and Cathepsins.

Roles of Immune-Mediator Regulation

Following cells are involved in the inflammatory part of atherosclerosis

- Macrophages
- Dendritic cells
- T cells

ROS IN ATHEROSCLEROSIS

ROS production causes oxidation of LDL in two mechanisms.

1. Extracellular - mediated by action of angiotensin II on macrophages and endothelial cells and stimulation of endothelial cells by TNF-α and other cytokines.
2. Intracellular - ROS production in the vascular smooth muscle cells occurs through the membrane-bound NAD(P)H oxidases, xanthine oxidase and uncoupled NO synthase. Angiotensin II is a powerful inducer of NAD(P)H oxidase and can stimulate the production of ROS eightfold in the VSMC. Intracellular ROS can serve as second messengers following hormonal stimuli [48,49] and act as intracellular signaling molecules in

vascular cells. They mediate phenotypic changes in vascular endothelial and smooth muscle cells regarding growth, apoptosis and survival. The extent of SMC growth response is determined by the net balance between proliferation and apoptosis due to ROS production.

Enzymes of arachidonic acid metabolism, xanthine oxidoreductase microsomal cytochrome P-450, and mitochondrial electron transport are the potential sources of ROS. Cytokines, physical forces and local hormones regulate the activity of these oxidases. Increased superoxide radical production in combination with NO produced by endothelium enhances availability of the harmful peroxynitrite. [49] Figure 4. Illustrates pathophysiology of atherosclerosis.

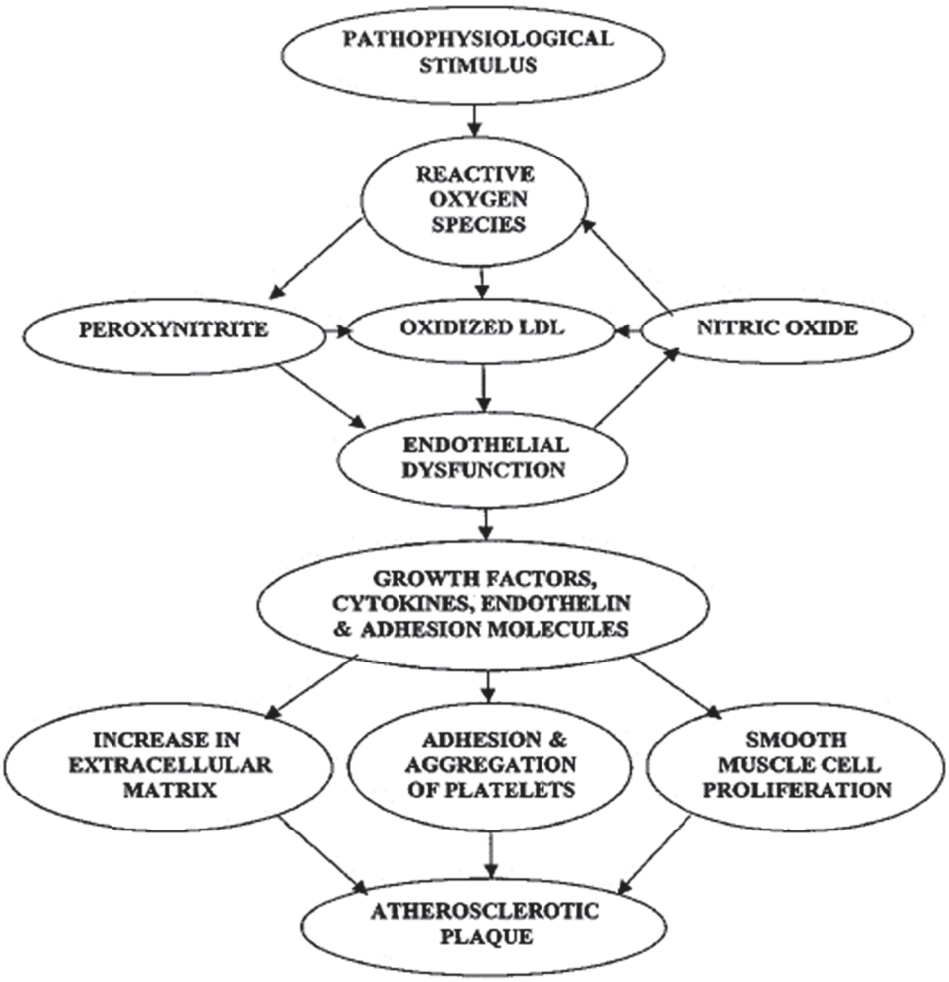


Figure 4.Pathophysiology of atherosclerosis

PATHOGENESIS OF ATHEROMA

Initiation

This pathological process starts with plaque formation which affects primarily the intima of large- and medium-sized arteries and slowly advances during an individual's lifetime finally manifests as an acute ischemic event.[50-52]

Progression

Following endothelial damage, monocytes migrate into the sub endothelial region to bind with adhesion molecules. Oxidized low-density lipoprotein (LDL)

particles also penetrate arterial wall. Macrophages digest oxidized LDL particles and transform into foam cells which causes the formation of fatty streak. The activated macrophages release monocyte chemo attractant protein 1, tumor necrosis factor α, and interleukins. These chemo attractants and cytokines mediate the process by recruitment of more macrophages and vascular smooth muscle cell which produce extracellular matrix components at the site of the plaque. Macrophages also release matrix metalloproteinases, which digest the extracellular matrix leading to plaque disruption.[51] In 99% of cases, it is clinically silent.[53]

Stability of Plaques and Tendency for Rupture

The stability of atherosclerotic plaques is variable. Characteristics which make them vulnerable or high risk are large size, thin fibrous cap, abundance of macrophages and T lymphocytes,[54,55] a relatively reduced numbers of smooth muscle cells,[56] increased levels of matrix metallo proteinases at the plaque,[57,58] eccentric configuration[59,60] increased neo vascularity of plaque and intra plaque bleeding.[59] Atherosclerotic plaques is heterogeneous in nature within the same individual.[60]

Inflammation, the important deciding factor of the "vulnerability" of atherosclerotic plaques[54, 61] is depended on increased activity of macrophages at the site of plaque. This increased activity leads to increased size of the lipid core and a thinning of the plaque cap which increase the tendency to rupture. There is a positive correlation between increased levels of C-reactive protein (CRP) with

the number of plaque ruptures[62] and may reflect the activity of these macrophages.[63]

Plaque Disruption, Thrombosis, and ACS

Atherosclerosis diminishes vascular lumen and reduces the perfusion of a tissue. Thrombus formation or hemorrhage in an atherosclerotic plaque further reduces the lumen of the vessel. The thromboembolic phenomenon associated with atherosclerosis that occurs due to rupture of unstable plaques is responsible for the acute coronary syndromes and unstable angina.

Non-critical coronary lesions (<50% stenosis in the diameter of the vessel by coronary angiographic studies) may be associated with sudden progression to severe or total obstruction of coronary arteries and may be responsible for two-thirds of cases of ACS.

Tissue factor and lipid molecular content of the plaque, the severity of the plaque rupture, the degree of inflammation at the site of the atheromatous plaque, vascularity of the area, and balance between pro thrombotic and antithrombotic tendencies are important determinants for the development of ACS.

Among the risk factors of coronary heart disease dyslipidemia in the form of increased total or LDL-Cholesterol, reduced HDL-Cholesterol and hypertriglyceridemia is the offender next to smoking.

Causes of dyslipidemia:

Congenital - familial hyper lipidemias

Acquired - high calorie intake,
diabetes mellitus,
obstructive jaundice,
nephrotic syndrome and
hypothyroidism.

Out of these thyroid gland is closely related to lipid metabolism. Thyroid gland exerts its actions on both heart and lipid metabolism.

THYROID GLAND

ANATOMY

Wharton coined the name "Glandulae Thyroidaeae" due to its relation to thyroid cartilage in 1656 and the fact that goiter is the disease of thyroid gland was established only in 1700.[64]

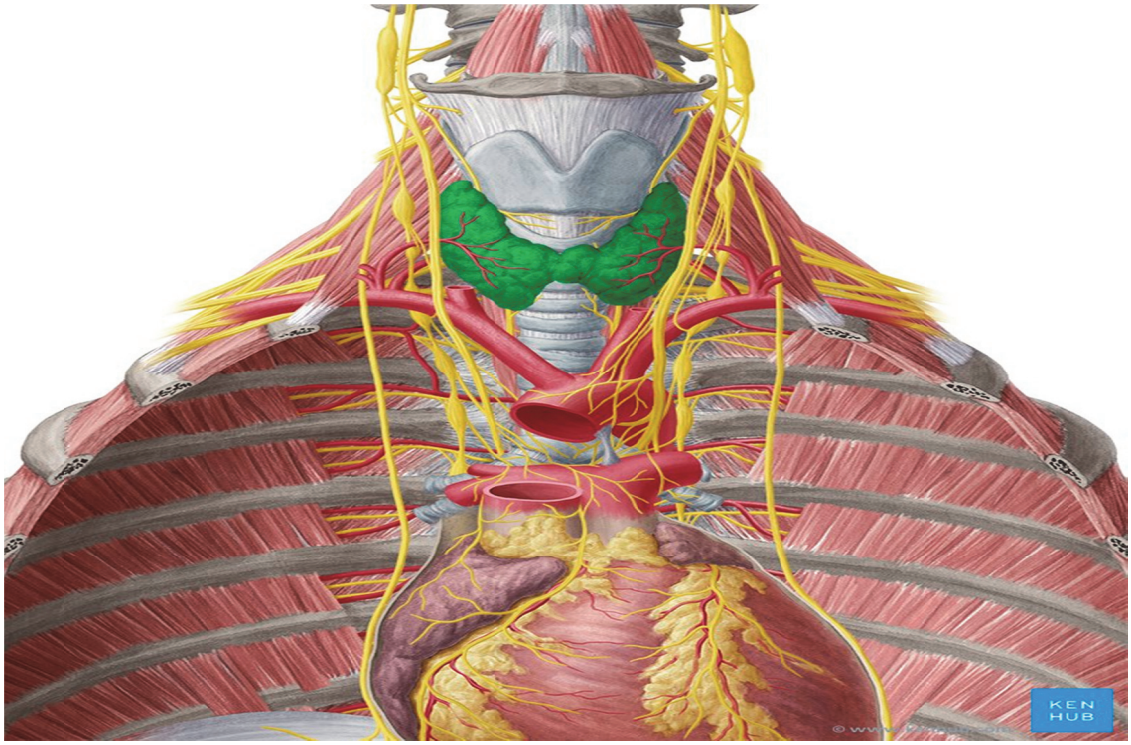


Figure 5.Thyroid gland – location and blood supply.

It is situated in anterolateral aspects of cervical trachea from oblique line of thyroid cartilage to 5th or 6th tracheal ring. It weighs about 25 g and 5cm× 2cm ×3cm in size and has two lobes. The part of gland which joins lobes at the level of 2nd to 5th tracheal cartilage is called isthmus. From the isthmus the pyramidal lobe may project upwards to the left of midline. Apart from own

capsule the gland is also enclosed by pre tracheal fascia which is thickened posteriorly and attached to the cricoid cartilage and upper tracheal rings (suspensory ligament of Berry).[65] This fixation and investment of gland by pre tracheal fascia are responsible for the movement of the gland up and down with larynx during swallowing. The thyroid gland is supplied by a pairs of superior and inferior thyroid arteries and drained by corresponding veins.[66] Figure 5. Shows the location and blood supply of thyroid gland.

Micro anatomy

Figure. 6 Histology of thyroid gland

Basic unit of thyroid gland is follicle. It is composed of follicular cells which surround the colloid. Follicular cells are connected by tight junctions. They are 0.02 to 0.9 mm in diameter and contain a rim that has a rich blood supply, nerve supply and lymphatic drainage. They surround the colloid which consists mainly thyroid hormone precursor proteins called thyroglobulin. [67]

Para follicular cells are present in spaces between follicles and scattered among follicular cells. They are also called C cells and secrete calcitonin. [68] Figure 6. Shows the histology of normal thyroid gland.

SYNTHESIS AND RELEASE OF THYROID HORMONES

IODINE TRAP

Thyroid hormone is synthesized from aromatic amino acid tyrosine. Iodination of tyrosine residues of thyroglobulin (Tg) produces thyroxin and triiodothyronine. Active transport of Iodide (I^-) from extra cellular fluid into thyroid gland through Na/I^- (sodium- iodide) symport (NIS) is the beginning step in thyroid hormone synthesis. After entry, cytoplasmic iodide moves into colloid via pendrin, a passive iodide transporting glycoprotein. Thyroglobulin is needed for the bio synthesis of thyroid hormone and account for 75% of total glandular protein. TSH is the principal stimulator of Tg synthesis. Thyroid transcription factor 1 (TTF1) interacts with Tg promoter to stimulate Tg mRNA synthesis.

OXIDATION OF IODINE

In the lacuna, the iodide is oxidized to iodine by Thyro peroxidase (TPO) enzyme. Hydrogen peroxide (H_2O_2) serves as the terminal electron acceptor forming $H_2O_2^-$. Hydrogen peroxidase is generated by dual oxidases (DUOX1and DUOX2) which has domains analogous to the domains found in Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxido reductases.

IODINATION

TPO catalyzes mono and di-iodination of tyrosine residues of thyroglobulin (Tg) and monoiodotyrosine (MIT) and diiodotyrosine (DIT) are formed.

COUPLING

T_3 is formed from one MIT and DIT with the transfer of one mono iodinated phenolic group to a DIT residue. T_4 is formed from two DIT residues with transfer of one di-iodinated phenolic group to another DIT residue.

STORAGE

At this stage both T_3 and T_4 are bound to thyroglobulin (Tg) which remains in the colloid providing reservoir of thyroid hormone.

RELEASE

On stimulation by TSH the apical pole of the follicular cells releases colloid into a vesicle by pinocytosis. Digestion of intra vesicular colloid (containing thyroglobulin) occurs in follicular cells after fusion of phagosome body with the primary lysosome. A secondary lysosome is formed by union of endocytosed Tg with primary lysosome. Digestion of Tg and release of T_3, T_4, MIT, DIT and amino acids occurs. Since T_3 and T_4 are lipophilic they diffuse through lysosomal membrane, cross the follicular cells and enter into capillaries.

SALVAGING IODINE

Iodine from MIT and DIT are removed by dehalogenase (Dhal) and iodide ions thus produced are reutilized for the synthesis of new thyroid hormones. Figure.7 Illustrates Thyroid hormone synthesis and release. Figure 8. Illustates structure of thyroid hormones

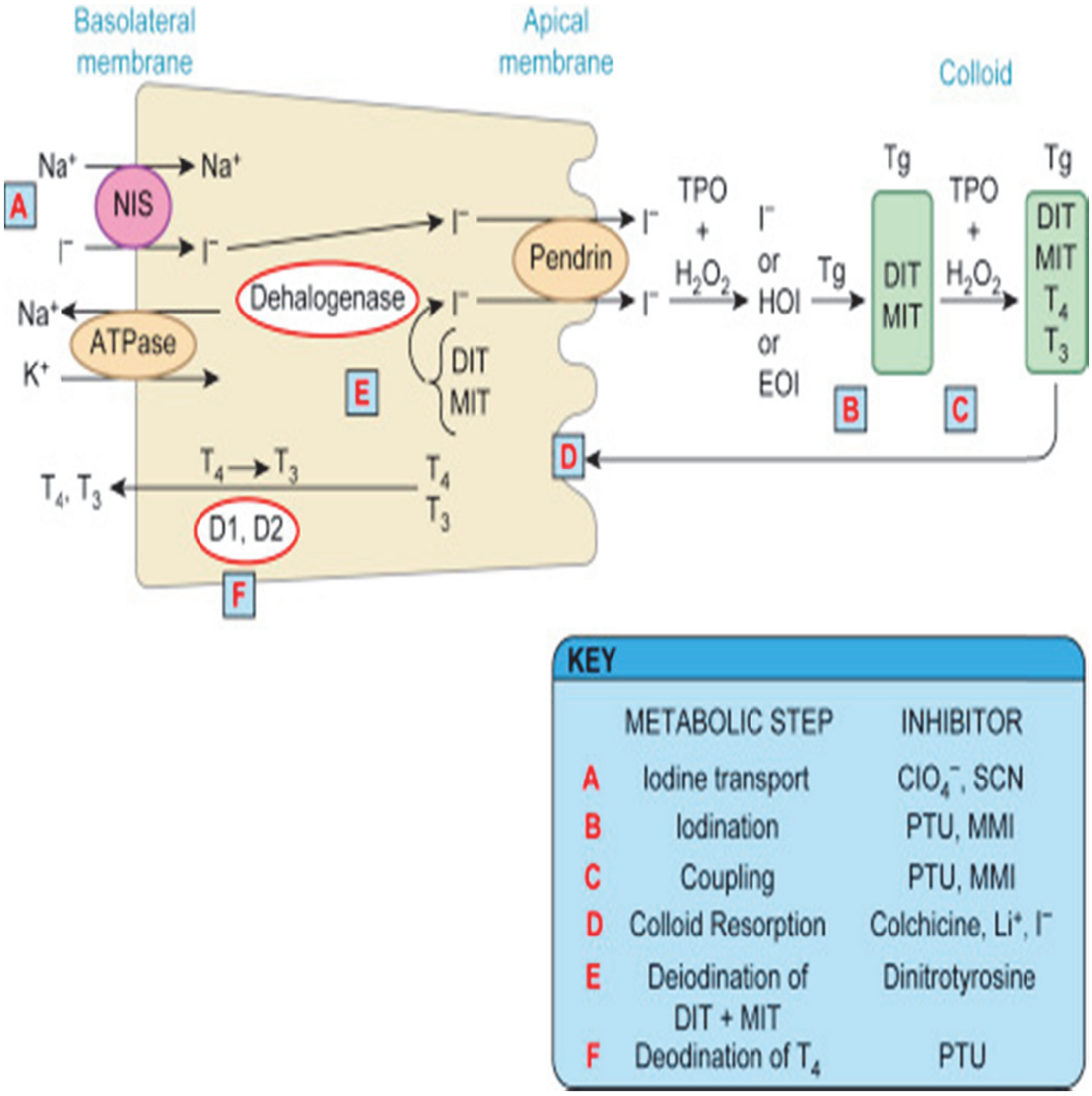


Figure.7 Thyroid hormone synthesis and release

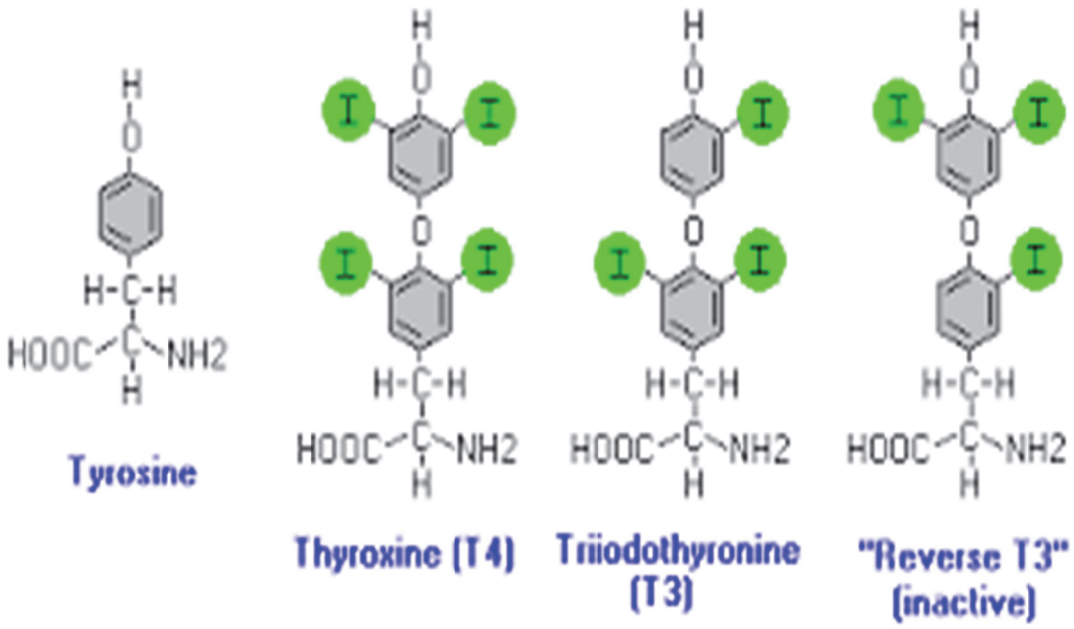


Figure.8 Structure of thyroid hormones

METABOLISM OF THYROID HORMONES

Thyroid hormones are highly protein bound. 0.03% of total T_4 and 0.3% of T_3 are free and biologically active. There are three kinds of deiodinases with nomenclature of type 1(D1), type 2 (D2) and type 3 (D3). These enzymes are homodimeric in nature having transmembrane and cytoplasmic domains.

Type 1(D1) is distributed in liver, kidney, thyroid and possibly the anterior pituitary gland and has inner ring deiodinase activity. Type (D2) deiodinase which acts on outer ring is expressed in brain, thyroid, anterior pituitary gland, brown fat, placental membranes, heart and skeletal muscles.[69]

Actions of thyroid hormones on heart

Thyroid hormones exert their action on all the cells and organs of the body.[70] In liver, kidney, and skeletal muscle T_4 is converted to T_3 by 5- mono deiodination.[71] Since cardiac myocyte is devoid of significant deiodinase activity

the musculature of heart is depended on T_3 only. So T_3 is transported into the myocyte (Figure.9)[72] and binds with thyroid hormone nuclear receptors (TRs).

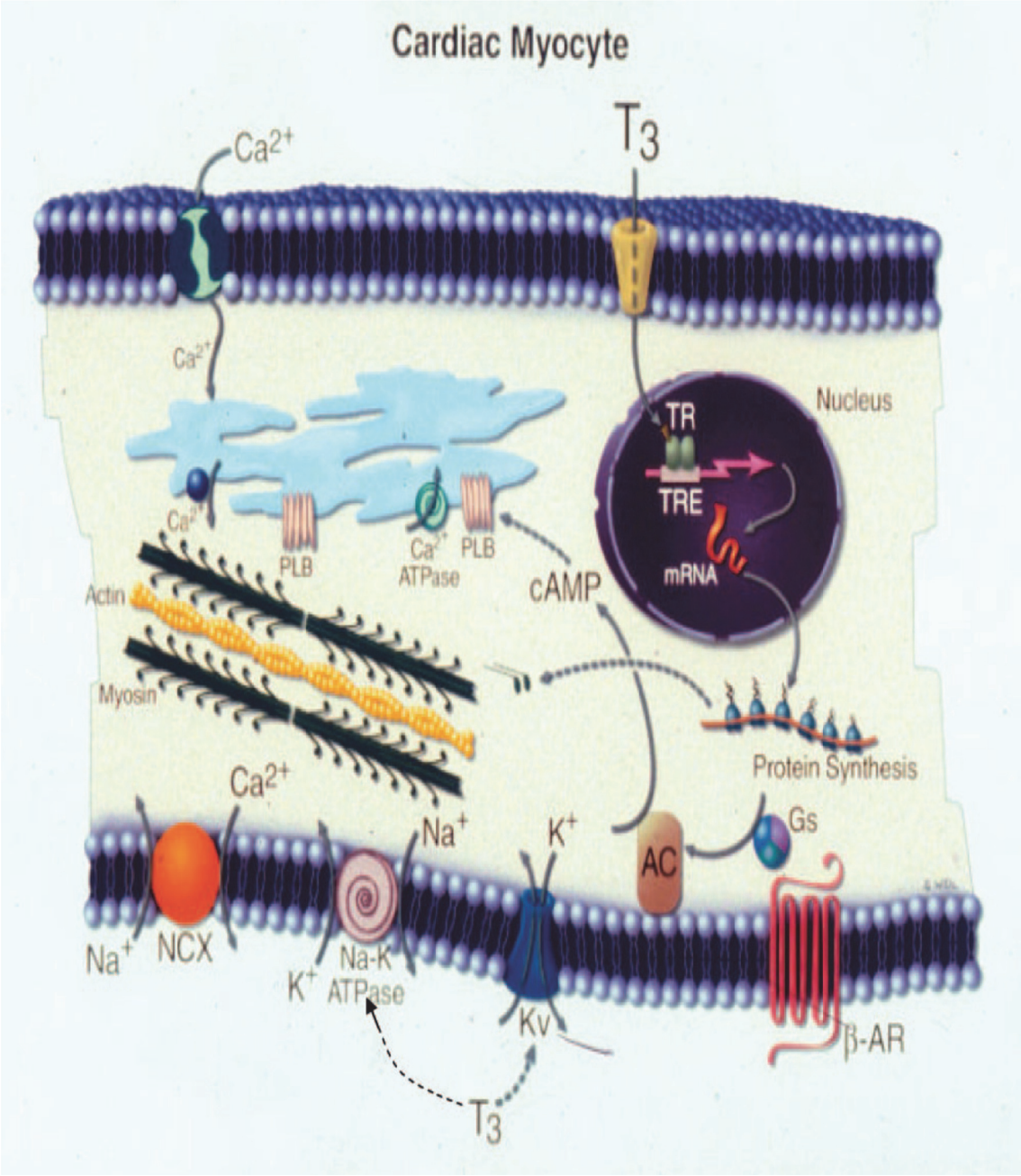


Figure. 9T_3 effects on the cardiac myocyte. (Circulation October 9, 2007: 1726)

(T_3 has both genomic and non-genomic effects on the cardiac myocyte. Genomic mechanisms involve T_3 binding to TRs, which regulate transcription of specific cardiac genes. Non-genomic mechanisms include direct modulation of membrane ion channels as indicated by the dashed arrows. AC- indicates adenylyl cyclase; β-AR - β adrenergic receptor; Gs - guanine nucleotide binding protein; Kv- voltage gated potassium channels; NCX-sodium calcium exchanger; and PLB - Phospholamban.)

These receptor proteins in turn binds with thyroid hormone response elements (TREs) in the promoter regions of positively regulated genes and mediates the induction of transcription.[73] Thyroid hormones nuclear receptors belong to the superfamily of steroid hormone receptors. TRs can bind to TREs in the absence as well as in the presence of ligand. TRs bind to TREs as homodimers or heterodimers with one of the three isoforms of retinoid X receptor (RXRα, RXRβ, or RXRγ). On binding to T_3, TRs induce transcription, and in the absence of T_3 they repress transcription.[74] Negatively regulated cardiac genes such as β-myosin heavy chain and phospholamban are induced in the absence of T_3 and repressed in the presence of T_3.[75]

Thyroid hormone effects on the cardiac myocyte are intimately associated with cardiac function via regulation of the expression of key structural and regulatory genes. The myosin heavy chain genes encode the 2 contractile protein isoforms of the thick filament in the cardiac myocyte. The sarcoplasmic reticulum Ca^{2+}-ATPase and its inhibitor, phospho lamban, regulate intracellular calcium cycling. Together they are largely responsible for enhanced contractile function and diastolic relaxation in the heart.[76] The β-adrenergic receptors and sodium potassium ATPase are also under T_3 regulation. Thyroid hormone also exerts thyroid hormone response elements (TREs) in the promoter regions of positively regulated genes.

Extra nuclear actions

The extra nuclear effects of T_3 on the cardiac muscle and on the systemic vessels do not involve TRE-mediated transcriptional events.[77]These effects are rapid and mediated through changes in characteristics of membrane ion channels for sodium, potassium, and calcium, effects on actin polymerization, adenine nucleotide translocator-1 in the mitochondrial membrane and many intracellular signaling pathways in the cardiac and vascular smooth muscle cells (VSM)[78]. Ultimately the combined nuclear and extra nuclear actions T_3 regulates cardiac function and cardiovascular hemodynamics.

THYROID HORMONES AND LIPID METABOLISM

The activity of the enzymes involved in the metabolism of lipoproteins and reverse cholesterol transport, such as hepatic lipase (HL), lipoprotein lipase (LPL), Cholesteryl-Esters Transfer Protein (CETP) and Lecithin-Cholesterol Acyl transferase (LCAT) is increased by thyroid hormones.

3-Hydroxy-3-Methyl-Glutaryl Coenzyme A Reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis is regulated by thyroid hormones like many hormones, such as insulin. In a state of hypothyroidism, HMGCR mRNA levels are diminished and therapy with thyroxin restores it to normal level. Thyroid hormone stimulates HMGCR transcription and increases its stability.

Stimulation of HMGCR by thyroid hormones occurs via SREBP-2 (Sterol Regulatory Element Binding Protein-2), a cholesterol sensing factor. Low Density Lipoprotein Cholesterol Receptor (LDL-R) and ATP-Binding Cassette Transporters (ABCA1 and ABCG5/8).

When intracellular cholesterol is reduced, thyroid hormone stimulates the transcription of SREBP2 gene and leads to increasing SREBP-2-mediated HMGCR gene transcription. Thyroid hormone-mediated LDL-R and BCA1/ABGG5/8 expression plays a major pathway for hepatic cholesterol clearance. It also diminishes the cholesterol through augmenting cholesterol clearance pathway. Cholesterol 7-hydroxylase (CYP7A1) is also regulated by thyroid hormones.

Effects on triglyceride

At transcription level, ANGPTL3 is negatively regulated by thyroid hormone, which is mediated by TRβ. Expression of this inhibitor causes increased TGL and total cholesterol. Thyroid hormone influences the maintenance of triglyceride levels by regulating APOA5gene transcription.

Apo A5 regulates TGL level by stimulating Lipoprotein Lipase mediated hydrolysis of triglycerides and inhibiting hepatic VLDL-TGL formation.[80]

REGULATION OF THYROID HORMONES

Synthesis and secretion of thyroid hormones are controlled by hypothalamus, anterior pituitary and follicular cells of thyroid gland through a negative feedback control system.

TRH concentration increase when thyroid hormone is deficient. TRH declines when there is excess thyroid hormone. Sensitivity of thyrotroph to thyroid hormone is modified by TRH. Following TRH stimulation there is reduced expression of thyroid hormone receptors in thyrotroph.

TSH increases size and numbers of thyroid follicle. TSH exerts its action by increasing activity of Sodium-Iodine symporter, increased synthesis of Thyroglobulin, TPO, H_2O_2 and NADPH.

Pinocytosis and degradation of colloid , release of T_3 and T_4 from Tg are observed on TSH stimulated thyrotrophs. Figure.10 shows regulation of thyroid hormones.

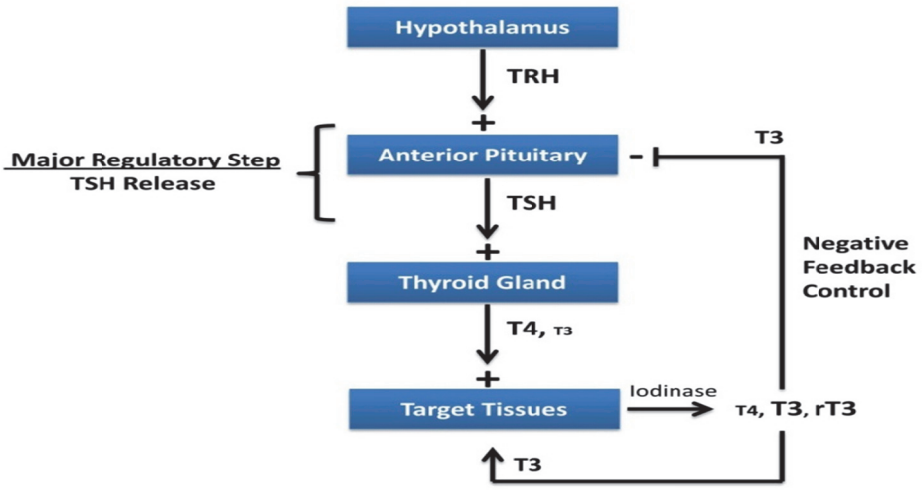


Figure 10. Regulation of thyroid hormones

PHYSIOLOGY OF AGING THYROID GLAND

Morphological studies done on thyroid gland revealed that degenerative processes occur in thyroid epithelium which results in flattening, reduction in the size of thyroid follicles and proliferation of lymphoid and fibrous connective tissue.

Consequences of these changes are reduction of the size of the thyroid gland and reduced Iodine uptake. In persons over 80 years the Iodine uptake falls by 40% in comparison with 30 years old persons. The daily thyroxin production is decreased per 20 μg. Conversely, the metabolism of thyroid hormones slow down due to the reduction in the activity of 5' Deiodinase-I which results in prolongation of the half-life of T_4 from 8 to 9.3 days without alteration in the serum T_4 concentration over time. The daily synthesis of T_3 reduces per 20 μg in males and 10 μg in females, and the serum concentration of T_3 in aged persons is reduced significantly. Studies done to evaluate hypothalamic-pituitary-thyroid axis exhibited various patterns of pituitary function: its preserved or reduced ability to secrete TSH following different stimuli.[81]

EUTHROID SICK SYNDROME

Definition

Abnormal levels of thyroid hormones, without clinical evidence of thyroid or pituitary gland disorder, are commonly seen in many systemic non thyroidal illnesses. The name "euthyroid sick syndrome" is used to describe abnormalities in thyroid function tests. The incidence may be 70%.Thyroid hormone changes

do not indicate thyroid disease. It is a response to the underlying illness, as these changes disappear on recovery from underlying illness. It is better called as "Non thyroidal illness syndrome"

Importance of knowledge of this response:

(a) Abnormal thyroid profile may mimic or mask intrinsic thyroid disease.

(b) The hormonal alteration in euthyroid sick syndrome represents an adaptive response to critical illness, where thyroxin is not helpful.

(c) The severity and nature of changes in thyroid profile have implications to assess the prognosis.

Patterns of Euthyroid Sick Syndrome

Four major types are described.

1. Low T3 Syndrome

This is the most common abnormality observed in about 70% of the in patients.[82] Serum FT_3 falls rapidly within 30 min to 24 hours of the onset of the causative illness. Levels of fall vary from undetectable to normal, and the mean value is approximately 40% of the normal level. The daily production of T_3 is decreased, while its clearance remains unchanged. The decreased conversion of thyroxin (T_4) to T_3 results from the inhibition of enzyme 5'-monodeiodinase (5'-MDI) activity, which catalyzes the deiodination of T_4 to T_3. Serum total T_4 and free T_4 (FT_4) are normal in patients with low T_3 syndrome. Generally serum TSH concentration and its response to Thyrotrophin releasing hormone (TRH)

are normal. However TSH level may elevate slightly, but returns to normal with recovery.

The reverse T_3 (rT_3) is elevated except in renal failure and traumatic brain injury. Daily production rate of rT_3 is normal. The increase in the serum rT_3 level is mainly due to its reduced metabolic clearance.

2. Low T_3 and T_4 syndrome

The low T_3 and T_4 syndrome is seen in critically ill. 30-50% of patients have low levels of T_3 and T_4. The total T_4 levels falls over 24-48 hours period. Serum TSH concentration is usually low and there will be blunted TRH responses. It may be due to impairment of TRH metabolism. TSH level rises with recovery, and may be transiently elevated until T_3 and T_4 levels are restored to normal. The rT_3 synthesis diminishes due to the decreased availability of its precursor T_4, but because of slow degradation rT_3 concentrations are frequently increased.

Several factors may contribute to low T_3 and T_4 levels.

These include:

(1) Reduced binding proteins, e.g., Thyroxin binding globulin (TBG), albumin and prealbumin especially in chronic liver disease and in renal dialysis,

(2) Abnormal TBG due to altered sialylation

(3) Circulating competitive binding inhibitors of T_4 to serum protein, including drugs furosemide in high doses, non-esterified fatty acids (NEFA) and metabolic products

(4) Decreased serum TSH, especially in patients treated with dopamine.

3. High T4 syndrome

This is very unusual and seen 1% of sick patients. It is observed in acute intermittent porphyria chronic active hepatitis and primary biliary cirrhosis acute psychiatric illness and patients on treatment with amiodarone and radio contrast usage for diagnostic purpose.

The serum concentration of FT_4 remains normal. The high serum T_4 level is usually the result of increased serum TBG. FT_3 concentration is typically decreased. The serum levels of rT_3 is also increased. This response due to both a high concentration of TBG and and a reduced metabolism of rT_3. The serum TSH is very low or undetectable, and TRH response is blunted.

4. Other abnormalities

Reduced nocturnal TSH surge, unrelated to circulating T4 and T3 levels, but probably related to hypothalamus

CAUSES OF EUTHYROID SICK SYNDROME

1. Medical

Acute myocardial infarction

Acute and chronic renal failure

Alcoholic liver disease

Hepatic cirrhosis

Malignancy

Obstructive airway disease

Diabetic ketoacidosis

2. Surgical

Spinal cord injury

Major trauma

Severe burns

During and after cardiopulmonary bypass

3. Infections

Viral hepatitis type A

Sepsis

Drugs

Amiodarone

Glucocorticoids

Propranolol

Radiographic contrast agents

Phenytoin

4. Miscellaneous

Anti-tuberculosis treatment

Hemodialysis

Clinical Significance

Low T_3 and T_4 level predict increased mortality from liver cirrhosis and congestive heart failure, thus indicating poor prognosis.

Evidences are pointing the existence of local hypothyroidism at tissue level because of low supplies of T_3 and T_4. Many patients with non-thyroidal illness are metabolically euthyroid in spite of the presence of low serum T_3 and T_4. Recent studies demonstrated that tissues of patients dying of Non thyroid illness contain lower levels of thyroid hormones than tissues of control subjects who die suddenly indicating the impending death. In contrast, studies also suggest that in Non-thyroid illness there will be increase in T_3 receptor number and binding affinity which maintains normal thyroid status in spite of reduced T_3.

Treatment

The majority of patients of euthyroid sick syndrome who are on recovery from their critical illness do not require any treatment. Thyroid function tests should be followed up.

SUB CLNICAL HYPOTHYROIDISM

DEFINITION

It is defined as a serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxin (T_4) within the reference range. [83]

Criteria for the diagnosis of sub clinical hypothyroidism

1. Other causes of raised TSH level, pre-existing thyroid illness and patients on Thyroxin treatment need to be excluded.
2. The reference limits for TSH should be standardized.
3. Methods used for the TSH assay should have a high functional sensitivity (at least 0.02 mU/L)

The panel of ATA/AACE concluded that range of 0.45-4.5 mIU/L should ultimately be adopted.

Epidemiology of Subclinical Hypothyroidism

An attempt to address the contentious issues of subclinical thyroid disease in a non-biased and systematic way was undertaken recently by efforts of the American Endocrine Society, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE). These societies co-sponsored a Consensus Development Conference in 2002 and contracted an independent consulting firm to review and summarize existing published evidences. The reports of epidemiology of this problem are more likely to be affected by the reference range of serum TSH which is used to define it. Studies

done in different parts of the world reviewed by the panel utilized different ranges. In the United States adult population the prevalence rate of subclinical hypothyroidism is 4-8.5%. This estimate may increase as age advances and differs between ethnic groups. Data of less consistency is available among males. The progression rate of SCH to overt or clinical hypothyroidism is approximately 2-5% per year. It is proportional to baseline serum TSH concentration and is more in individuals with anti-thyroid antibodies. Despite the impact of thyroid antibody positivity on the epidemiology of subclinical hypothyroidism, the panel did not advise the use of anti-thyroid peroxidase (TPO) antibodies. This differs from recommendations by the Royal College of Physicians (RCP), AACE, ATA and Australian thyroidologists.

Studies about the consequences of subclinical hypothyroidism

In general there was insufficient or no evidence to support an association between subclinical hypothyroidism and clinical conditions. The exception was dyslipidemia, particularly in patients with a TSH >10 mU/L. Some studies found T_4 replacement can improve dyslipidemia. But it is not confirmed by other studies.

The panel concluded that clinically significant relationship between subclinical hypothyroidism and adverse cardiac events or cardiac dysfunction was insufficient. Only a single large cross-sectional study gave the conclusion that subclinical hypothyroidism was a risk factor for atherosclerosis and myocardial infarction.

Evidences are insufficient for neuropsychiatric and systemic hypothyroid symptoms in SCH. A large cross-sectional study demonstrated that participants with subclinical hypothyroidism had more symptoms than euthyroid individuals, but less symptoms than patients with overt hypothyroid participants and distinction was not possible between untreated subclinical hypothyroidism and undertreated overt hypothyroidism. Other studies have not confirmed this association. Randomized control trials which included patients with a TSH less than 10 μIU/ml, found no improvement in symptoms.

Like many risk factors overt hypothyroidism has an impact on cardio vascular events through changes in lipid profile. Even though there are conflicting reports regarding effects of subclinical hypothyroidism on lipid profile, its progression to overt hypothyroidism is well documented. So, it is worth to do thyroid function tests in ACS patients.

MATERIALS AND METHODS

AIMS and OBJECTIVES OF THE STUDY:

- To know the prevalence of subclinical hypothyroidism in patients with acute coronary syndrome.
- To compare serum lipid profile changes in Euthyroid with Subclinical hypothyroid patients in acute coronary syndrome.
- To correlate the lipid profile changes with subclinical hypothyroidism in patients with acute coronary syndrome.

STUDY DESIGN

The study was conducted as a cross sectional study on 100 patients with acute coronary syndrome at Government Mohan Kumaramangalam Medical College Hospital, Salem during the period between December 2017 –May 2018.The patients were admitted at IMCU or ICCU under the supervision of cardiology department. Informed consent was obtained from all patients. All procedures concerning patients were permitted by the Institutional Ethical Committee.

STUDY POPULATION:

INCLUSION CRITERIA:

100 cases of ACS giving consent irrespective of age, sex, race and clinical severity were included.

EXCLUSION CRITERIA:

1. The patients who refused to give consent.
2. Those having thyroid disorders.
3. Patients known to have neoplasia anywhere in the body, chronic kidney disease, obstructive air way disease, chronic liver disease or active infection
4. Patients taking steroids, amiodarone or lithium and
5. Patients for whom iodinated contrast medium was given in the recent past. (2 weeks)

Two groups were made depending on the characters of chest pain, ECG findings and the results of CK-MB level.

STUDY GROUPS

Group1. Non ST-Elevation ACS: (Unstable angina/ non STEMI)

- Cases with pain at rest or with minimal exertion lasting >10 minutes or
- Severe chest pain of new onset (i.e., within the prior 4-6 weeks); or
- Pain with a crescendo pattern (i.e. more prolonged, severe, or frequent than before)
- ECG findings of ST depression / T wave inversion with normal or elevated serum CK-MB levels.

At the time of presentation, patients with UA and NSTEMI can be indistinguishable and therefore are considered together in this guideline. [85] The

diagnosis of NSTEMI was established if a patient with the clinical features of UA develops evidence of myocardial necrosis, as reflected in elevated CK-MB.[85]

Group 2: ST elevation MI

Cases with symptoms of myocardial ischemia combined with ST elevation in electro cardiogram and elevated CK-MB levels, indicative of myocardial necrosis were included in STEMI group.

The following investigations were done for all the patients in this study.

1. Complete Blood Count
2. ECG in all leads
3. Creatine Kinase- MB iso enzyme
4. Random blood glucose level (Fasting and Post prandial if necessary)
5. Urea and Creatinine
6. Fasting lipid profile – total cholesterol, triglycerides, HDL-Cholesterol.
7. FT_3, FT_4 and TSH assay
8. Echocardiography (after stabilizing patients)

SAMPLE COLLECTION:

For this study 4ml of fasting venous blood was collected from each of the hundred ACS patients under sterile conditions within 24 hours of admission with explicit informed consent.

I. 2ml of blood was collected in plain vials. Serum was separated after centrifugation at 3000 rpm for 10 minutes and aliquoted into eppendorf tubes. They were stored at -20°C and were not thawed until the batch was analyzed for FT_3, FT_4 and TSH.

II. 2ml of blood was collected in another set of plain vials and serum was separated after centrifugation at 3000 rpm for 10 minutes. Estimations of glucose, urea, creatinine,

CK-MB, total cholesterol, triglycerides and HDL-Cholesterol were done with ERBA XL-640 auto analyzer. Calibration was done with ERBA – Multical

ESTIMATION OF GLUCOSE

Method : Glucose oxidase peroxidase (GOD/POD) (End Point)

Kit Used : ERBA

Principle

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{Glucose oxidase}} \text{Gluconic acid} + H_2O$$

$$H_2O_2 + \text{Phenol} + 4AAP \xrightarrow{\text{Peroxidase}} \text{Quinoneimine dye} + H_2O$$

The intensity of pink colored Quinoneimine dye is proportionate to glucose concentration and was measured at 505nm.

Reagent Composition

Active ingredients

Glucose oxidase → ≥ 20000U/L

Peroxidase → 800U/L

Phenol → 10 mmol/L

Tris -Phosphate buffer → 50 mmol/L

Mutarotase → ≥1000 U/L

ASSAY PARAMETERS

Reagent volume -200µl

Sample volume -2µl

Reaction - increasing

Reference range

Fasting glucose - 70-100mg/dl

Post prandial glucose - 110-140mg/dl

ESTIMATION OF BLOOD UREA

KIT: ERBA

Method: UV - GLDH

Principle:

The test is performed as a kinetic assay in which the initial rate of the reaction is linear for a limited period of time. Urea is hydrolyzed by urease to NH_3 and CO_2. The NH_3 produced combines with alpha-keto glutarate and NADH in the occurrence of glutamate dehydrogenase and produces glutamate and NAD.

$$\text{Urea} + H_2O \xrightarrow{\text{Urease}} 2NH_3 + CO_2$$

$$NH_3 + \text{NADH} + \text{alpha keto glutarate} \xrightarrow{\text{GLDH}} \text{L- Glutamate} + NAD^+$$

The initial rate of decrease in absorbance is directly proportional to the urea concentration in the sample. Absorbance is measured at 340nm.

Reagents

Reagent 1.

Tris buffer – 100mmol/L

Alpha keto glutarate- 5.49mmol/L

Reagent 2.

NADH

Also contains non –reactive fillers and stabilizers

Assay Parameters

Reagent 1 - 160 µl

Reagent 2 - 40 µl

Sample volume - 2 µl

Reaction - decreasing

Primary wave length for measurement of absorbance – 340nm

Reference range 15-40mg/dl

ESTIMATION OF SERUM CREATININE

Kit used : ERBA

METHOD : Modified Jaffe's Method

Principle: Creatinine in alkaline solution reacts with picrate to form an orange yellow compound. The color is proportional to the concentration of creatinine in the sample when measured at 505nm.

Reagent composition:

Reagent I:

Picric acid – 26mmol/L

Reagent II:

Sodium hydroxide – 240 mmol/L

Assay parameter

Reagent I -160 µl

Reagent II - 40 µl

Sample volume - 10 µl

Reaction – increasing

Reference range 0.7-1.4mg/dl

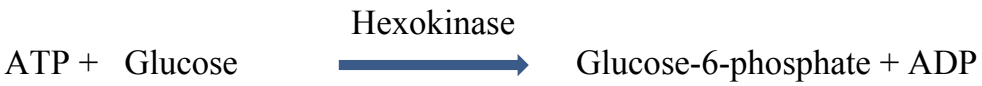
ESTIMATION OF CK-MB

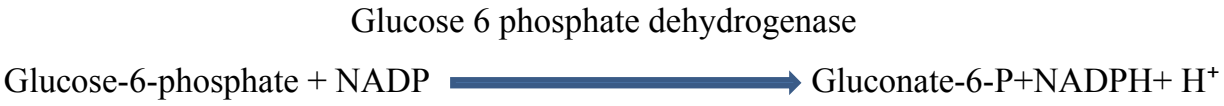
KIT-ERBA

METHOD-KINETIC

PRINCIPLE

Specific antibodies against CK-M inhibit the complete CKMM activity and the CK-M subunit of CKMB. Only CK-B activity is measured.





REAGENT COMPOSITION

R1

Imidazole buffer, pH 6.1	-125 mmol/l
Glucose	-25 mmol/l
Magnesium acetate	-12.5 mmol/l
EDTA	-2 mmol/l
N-acetyl-L-cysteine	-25 mmol/l
NADP	-2.4 mmol/l
Hexokinase	> 6.8 U/ml

Anti-CK antibodies (goat) blocking capacity up to 2000 U/l CK-MM

R2

Imidazole buffer, pH 8.9;	125 mmol/l
ADP ;	15.2 mmol/l
Creatine phosphate	250 mmol/l
AMP	25 mmol/l
Diadenosine pentaphosphate	103 µmol/l

D-glucose-6-phosphate-dehydrogenase > 8.8 U/ml

The rate of absorbance change at 340 nm is directly proportional to half of CK-MB activity (B subunit activity).

ASSAY PARAMETER

Sample volume - 8 µl

Reagent 1 - 160 µl

Reagent 2 - 40 µl

Assay type – Rate –A

Reference range

Less than 25 IU/L at the temperature of 37 C

CK-MB activity ranging between 6% and 25 % of the total CK activity

ESTIMATION OF CHOLESTEROL

KIT- ERBA

METHOD – 1point

Principle.

$$\text{Cholesterol ester} \xrightarrow{\text{Cholesterol Esterase}} \text{Cholesterol + Fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{Cholesterol Oxidase}} \text{Cholest-4-en-3-one} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + \text{4Amino antipyrin} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine Dye (Chromophore)} + 4H_2O$$

The Absorbance is proportional to Quinoe imine dye which may be measured at 505nm.

REAGENT COMPOSITION

Good‘s Buffer -50 mmol/l

Phenol 5 - mmol/l

4-aminoantipyrine -0.3 mmol/l

Cholesterol esterase ≥ 200 U/l

Cholesterol oxidase ≥ 50 U/l

Peroxidase ≥ 3 kU/l

Assay parameter

Reagent 1 - 200 µl

Sample volume - 2 µl

Reaction –increasing

Reference range

Adult

Desirable < 200 mg/dl

Borderline high 200-239mg/dl

High > 239 mg/dl

Child

Desirable < 170mg/dl

Borderline 170-199mg/dl

High > 199 mg/dl

ESTIMATION OF TRIGLYCERIDES.

KIT- ERBA

Method – Glycerol -3-phosphate oxidase method

PRINCIPLE

The following s reactions occur in the assay system

$$\text{Triglycerides} + H_2O \xrightarrow{\text{Lipoprotein Lipase}} \text{Glycerol} + \text{Free Fatty acids}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{Glycerol Kinase}} \text{Glycerol-3-phosphate} + \text{ADP}$$

$$\text{Glycerol-3-phosphate} + O_2 \xrightarrow{\text{Glycerol-3-Phosphate Oxidase}} \text{DAP} + H_2O_2$$

$$H_2O_2 + \text{4AAP} + \text{TOOS} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine} + H_2O$$

(Coloring dye)

Absorbance of this dye is proportional to the concentration present in the sample.

REAGENT COMPOSITION

R1

PIPES buffer (pH 7.0) 50 mmol/l

TOOS 0.48 mmol/l

Mg^{++} 60 mmol/l

ATP 2.85 mmol/l

Glycerol kinase ≥ 1.5 U/l

Glycerol-3-phosphate-Oxidase ≥ 6 U/l

R2

Peroxidase ≥ 15 U/l

Lipoprotein lipase ≥ 25U/l

4-Aminoantipyrine 0.5 mmol / l

ASSAY PROCEDURE

Wavelength 500 (546) nm

Reaction – increasing

Reagent 1 160 µl

Reagent 2 40 µl

Sample volume 2 µl

REFERENCE RANGE

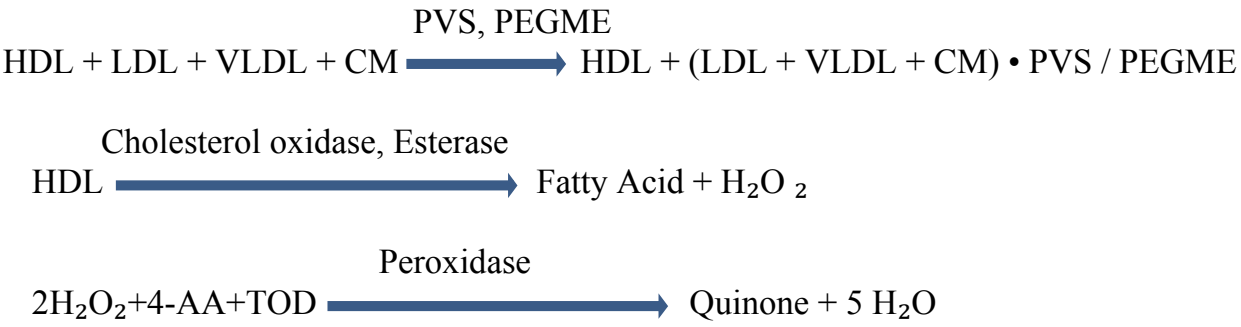
Preferable range – less than 150mg/dl

ESTIMATION OF HDL-CHOLESTEROL

KIT - ERBA

PRINCIPLE

Modified polyvinyl sulfonic acid (PVS) and poly ethylene glycol-methyl ether (PEGME) coupled classic precipitation method with the improvements LDL, VLDL and chylomicron (CM) react with PVS and PEGME and the reaction causes inaccessibility of LDL, VLDL and CM by cholesterol oxidase (CHOD) and cholesterol esterase (CHER).The enzymes selectively react with HDL to produce H_2O_2 which is detected through a Trinder reaction.



REAGENT COMPOSITION

R1 MES buffer (pH 6.5) - 6.5 mmol/l

TODB N, N-Bis(4-sulfobutyl)-3-methylaniline - 3 mmol/l

Polyvinyl sulfonic acid -50 mg/l

Polyethylene-glycol-methyl ester -30 ml/l

$MgCl_2$ - 2 mmol/l

R2 MES buffer (pH 6.5) -50 mmol/l

Cholesterol esterase - 5 kU/l

Cholesterol oxidase- 20 kU/l

Peroxidase 5 kU/l

4-aminoantipyrine 0.9 g/l

Detergent 0.5 %

R3 CAL

HDL/LDL Calibrator

ASSAY PROCEDURE

Wavelength: 600/700 nm

Reaction- increasing

Assay type – 2 - point.

Reagent-1 180 µl

Reagent-2 60 µl

Sample volume 2 µl

Reference range

Adult male- 35.3-79.5mg/dl

Adult female 42- 88mg/dl

Thyroid profile Assay

INSTUMENTS -ROBONIK Elisa Reader and Washer

Free T_3 Assay

KIT - RecombiLISA

TEST PRINCIPLE

It is a competitive solid-phase enzyme-linked immunosorbent assay for the quantitative measurement of FT_3in human serum.

Materials and reagents needed

Anti-FT_3Ab coated micro wells

FT_3 Calibrators (0, 1.5, 4.5,9,18,32 pgs. /ml)

HRP conjugates

Wash buffer

TMB substrate

Stop solution

ELISA working sheet

Procedure

1. Desired number of micro wells were removed and secured in the micro plate frame.
2. 50µl of FT_3 calibrators and patient specimens were added into the assigned wells.
3. 100µl of HRP-T3 was dispensed in each well except the Blank Wells.
4. The micro plate gently was rocked for 20 seconds, and then covered with the plate with micro plate sealer.
5. The wells were incubated at room temperature (20-28°C) for 60 minutes.
6. Wash Step (automated washing**):** Automatic plate washer was calibrated to ensure efficient washing. Each well was filled with 350µl working wash buffer and soaked for 20-30 seconds. All wells were aspirated completely. Repeated for 4 more times.
7. 100 µl of TMB Substrate was added into each well, including the Blank Well. Gentle rocking of the micro plate for 20 seconds to ensure thorough mixing was done.
8. Micro plate was incubated at room temperature (20-28°C) in dark for 15 minutes.
9. 100 µl of Stop Solution was added into each well to stop the reaction, including the Blank Well. Gentle mixing for 20 seconds was done. It is

important to make sure that all the blue color changes completely to a yellow color.

10. Micro plate reader was set for wavelength at 450 nm. The absorbance (OD) of each well against the Blank Well within 15 minutes after adding Stop Solution was measured.

Free T_4 assay

KIT – RecombiLISA

Materials and reagents needed

Anti-FT_4 Ab coated micro wells

FT_4 Calibrators (0,0.62,1.2,1.8,3.8,7.5 ng /dl)

HRP conjugates

Wash buffer

TMB substrate

Stop solution

ELISA working sheet

TEST PRINCIPLE

It is a competitive solid-phase enzyme-linked immunosorbent assay for the quantitative measurement of FT3 in human serum.

Procedure

1. Desired number of micro wells were removed and secured in the micro plate frame.

2. 50µL of fT4 calibrators and patient specimens were added into the assigned wells.
3. 100µL of HRP-T4 Conjugate was dispensed into each well except the Blank Wells.
4. Micro plate was rocked gently for 20 seconds, and then covered with a sealer.
5. The wells were incubated at room temperature (20-28°C) for 60 minutes.
6. Wash Step (performed with automated washing):

   Automated washing: Automatic plate washer must be calibrated to ensure efficient washing. Each well should be filled with 350µL diluted wash buffer and soak for 20-30 seconds. All wells should be aspirated completely repeated 4 more times.
7. 100µL of TMB Substrate was added into each well, including the Blank Well.

   The micro plate was rocked gently for 20 seconds to ensure thorough mixing.
8. Incubation was done at room temperature (20-28°C) in dark for 15 minutes.
9. 100µl of Stop Solution was added to each well including the Blank Well. Gentle mixing was done for 20 seconds. It is important to make sure that all the blue color changes completely to a yellow color.

10. Micro plate reader was set at wavelength at 450 nm. The absorbance (OD) of each well against the Blank well was measured within 15 minutes after adding Stop Solution.

TSH ASSAY

KIT – RecombiLISA

PRINCIPLE

Solid phase enzyme linked immune sorbent assay based on sandwich technique.

PROCEDURE

The test samples and HRP-anti-TSH conjugates are incubated simultaneously with the coated micro wells. The TSH in serum reacts to the anti-β TSH antibody coated on the micro well surface as well as the HRP-anti-TSH conjugates, forming an antibody sandwich immune complex. Unbound conjugates are then removed by washing. The presence of the conjugate complex is identified by development of a blue color upon additional incubation with substrate. The reaction is terminated with Stop Solution and the absorbance determined using a spectrophotometer at 450/620-690 nm.

A standard curve is generated by plotting the absorbance at 450/620-690 nm wavelength versus the respective TSH concentration for each standard. The concentration of TSH in the serum is calculated from the curve.

1. Desired quantity of strips were taken out and positioned in the micro plate frame.

2. 50 µl of the TSH Standards and patient specimen were added in the assigned wells.
3. 50 µl of HRP-anti-TSH conjugates was added into each the well except the Blank Wells.
4. Gentle Rocking of the micro plate for 30 seconds covering the plate with a micro plate sealer was done.
5. Incubation of the wells at 37ºC for 60 minutes was done.
6. Careful removal of the the incubation mixture by emptying the solution into a waste container, filling each well with diluted Wash Buffer and shaking for 20-30 seconds were done. Washing was done 4 more times. To remove residual liquid tapping on absorbent paper was done.
7. 100 µl of TMB Substrate was added into each well, including the Blank Well and gentle mixing was doe.
8. Incubation in dark room at room temperature (20-25ºC) for 20 minutes was done.
9. 100 µl of Stop Solution was added to each well gentle mixing was done for 30 seconds.

   It is important to ensure that all the blue color completely changes to a color yellow.
10. Micro plate reader was set for the wavelength at 450 nm and the absorbance (OD) of each well against the Blank Well was measured within 15 minutes after adding Stop solution.

The reference ranges of these tests made in the department of biochemistry at Government mohan kumaramangalam medical college hospital are shown in table 2. below:

TABLE 2. Reference ranges for the biochemical parameters estimated in this study.

Biochemical Test	Reference Range
Fasting blood glucose	70-100mg/dl
Post prandial glucose	110-140mg/dl
Urea	15-40mg/dl
Creatinine	0.7-1.4mg/dl
CK-MB	0-25 IU/L
Cholesterol	Less than 200mg/dl
Triglycerides	Less than 150mg/dl
HDL-C	30-60mg/dl
Free T3	1.16 - 4.34 pg/dl
Free T4	0.58-2 ng/ml
TSH	0.4 - 5 μIU/ml
LDL-Cholesterol calculated by Friedewald equation [84]	Less than 130mg/dl

STATISTICAL ANALYSIS

- Graph pad prism version 7 was used for statistical analysis.
- P value less than 0.05 was considered as statistically significant.
- Data of age and fasting blood glucose level of whole study population were compared with their TSH level.
- Comparisons between data of TSH and lipid profiles of euthyroid group and subclinical hypothyroid group were done with paired *t* test.
- Correlation between data of lipid and thyroid profile of subclinical hypothyroid patients and euthyroid patients was made with Pearson's correlation analysis.
- Categorical data (different age groups, gender, clinical severity types) were analyzed with Chi square or fisher's exact test

RESULTS

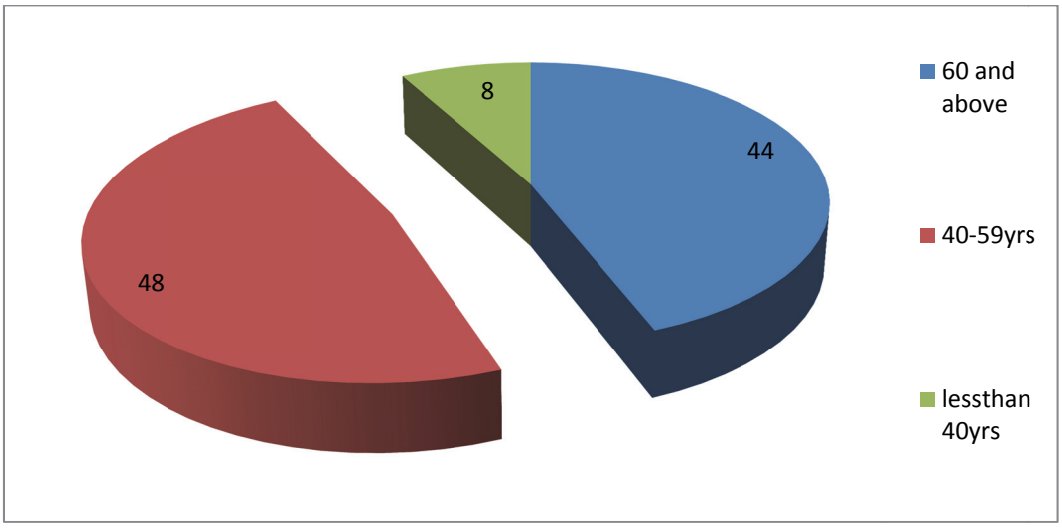
The Mean age of the study population was 57.05 ± 11.15years (range 34 – 95 years). 72 (72%) were males and 28 (28%) were females. 61patients (61%) had presented with STEMI and 39 patients (39%) presented with Non ST Elevation ACS (NSTEMI and UA). These data are showed in Table 3**.**

Table 3: Baseline characteristics and presentation of the study population.

Variables			**Total patients - 100**	
			No of patients	**Percentage**
Age	Mean ± SD 57.05 ± 11.15 Range 34- 95 years	60 yrs. and above	44	44
		40-59 yrs.	48	48
		Less than 40 yrs.	8	8
Gender	Male		72	72
	Female		28	28
ACS type	STEMI		61	61
	Non ST Elevation ACS		39	39

Out of 100 patients included in this study 44 were in the age of 60 years and above; 48 were between 40 -59 years of age; 8 patients were below the age of 40 years. It is shown in figure 11.

Figure11 . Age wise distribution of ACS patients



Distribution of ACS patients according and their gender and clinical severity are shown in figures 12 and 13 respectively.

Figure 12. Gender distribution of ACS patients in this study.

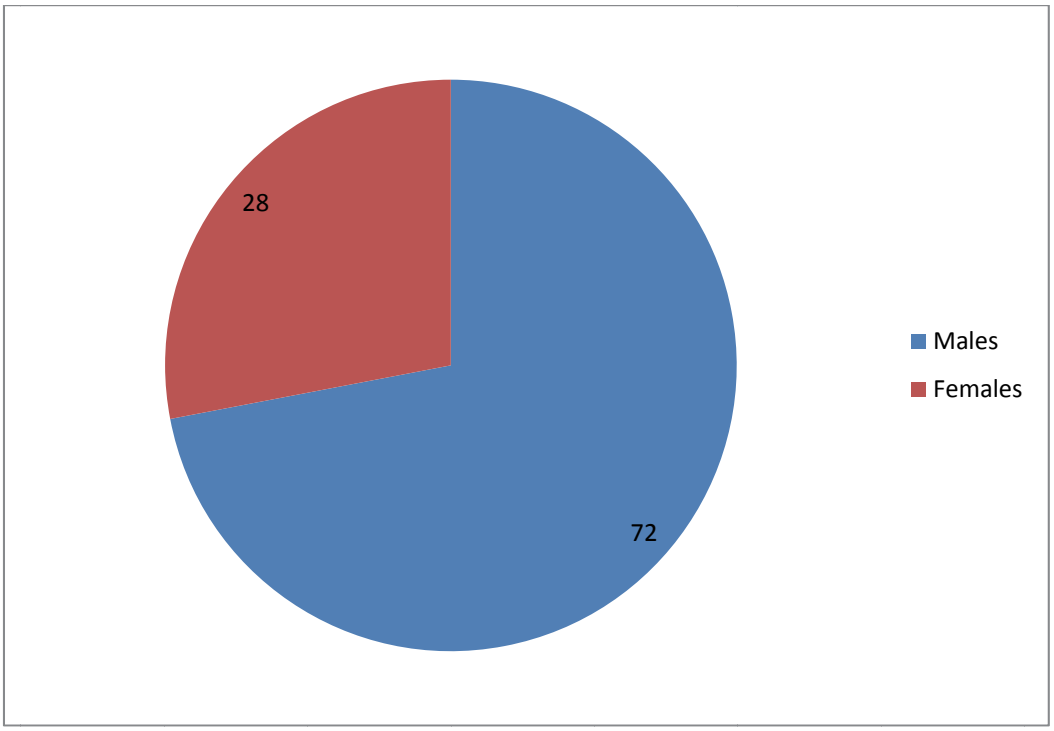
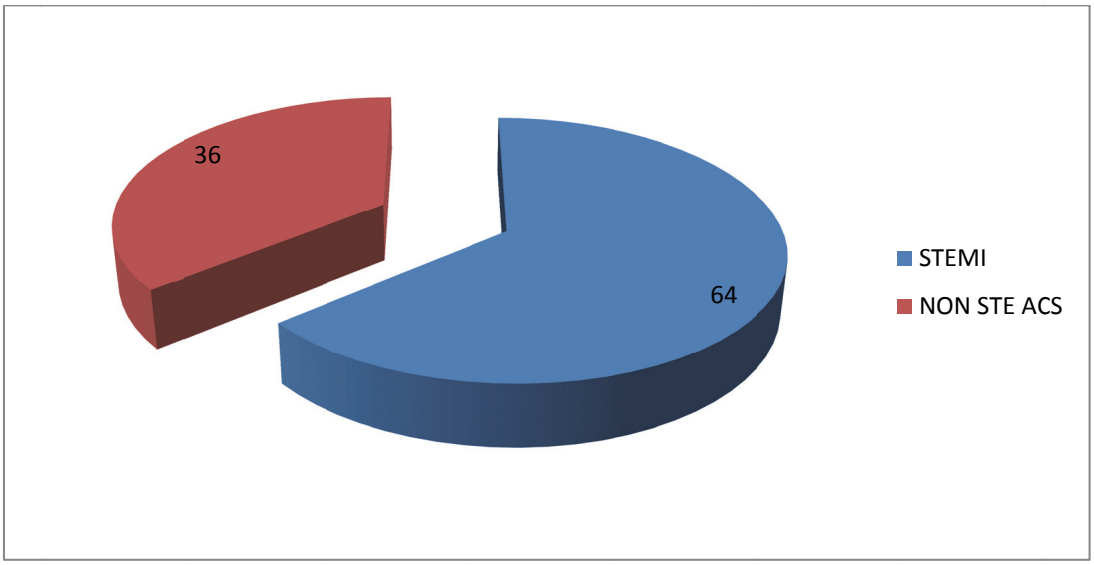


Figure 13. Distribution of clinical severity in ACS patients



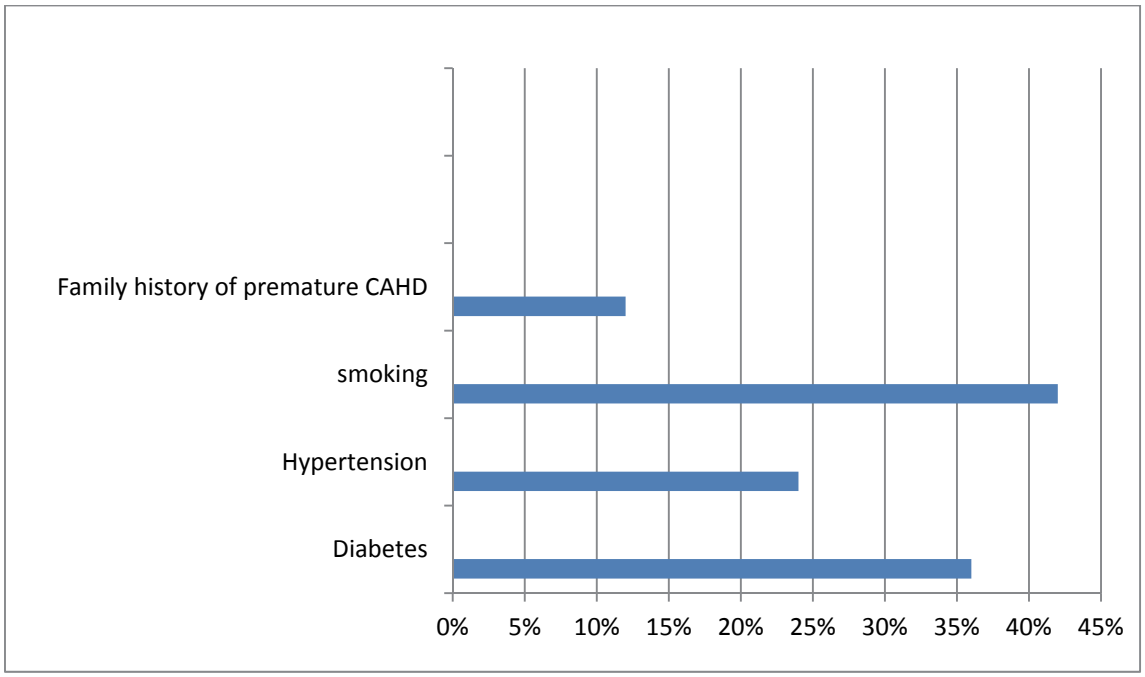
Risk factors in ACS patients

Out of 100 patients 36 patients were diabetics; 24 patients were hypertensive; 12 patients had family history of pre mature of coronary artey heart disease and 42 patients were smokers. This is shown in Table 4 and figure 14.

Table 4. Risk factors in ACS patients in the study

No	Risk factors	No	Percentage
1	Diabetes mellitus	36	36
2	Hypertension	24	24
3	Smoking	12	12
4	Family history of premature CAHD	42	42

Figure 14. Distribution of Risk factor in ACS patients



Gender, age and clinical severity in SCH patients

The prevalence of Sub clinical hyothyroidism in patients aged 60 and above was 4.54% and 8.93% in patients aged below 60 years.There was no statistical difference in prevalence of subclinical hypothyroidism between these groups. Regarding the gender, prevalence of SCH in males was 5.56% and 10.71% in females.There was no statistical difference in males and females.

The prevalence of SCH in STEMI patients was 8.2%. It was 5.13% in Non ST Elevation ACS. There was no statistical difference in these clinical severity groups. It is shown in Table 5.

Table 5. Age, gender and severity distribution of SCH Patients

Variable	Age	Total No	No of SCH	Percentage	P value
Age	60 and above	44	2	4.54%	0.461 ns
	Less than 60	56	5	8.93%	
Gender	Males	72	4	5.56%	0.3963 ns
	Females	28	3	10.71%	
ACS Type	STEMI	61	5	8.2%	0.7021 ns
	Non ST Elevation ACS	39	2	5.13%	

Lipid profile of patients with different thyroid status

Patients with euthyroid profile had hypercholesterolemia in 33.3%, hypertriglyceridemia in 34%, increased LDL-C level in 24.6% and lowered HDL in 26.1%.

In subclinical hypothyroid patients hypercholesterolemia was seen in 14.3% and hypertriglyceridemia in 42.9%. High level of LDL-C level was seen in 14.3% and HDL-C level was decreased in 28.6%of SCH patients. Tables - 6&7 and Figures 15&16 Illustrates the lipid profile abnormalities in different thyroid states in the whole study population.

Table 6. Lipid profile changes in different thyroid states

Thyroid state	ACS type & No	High TC			High TGL			High LDL - C			Low HDL - C		
		Gender		No	Gender		No	Gender		No	Gender		No
Euthyroidism Total- 69	STEMI (38)	M	F	23	M	F	24	M	F	17	M	F	18
		13	7		13	2		10	1		8	1	
	Non STE ACS (31)	2	1		4	5		4	2		8	1	
Subclinical Hypothyroidism Total - 7	STEMI (5)	1	-	1	1	1	3	1	-	1	-	2	2
	Non STE ACS (2)	-	-		-	1		-	-		-	-	
Subclinical hyper-thyroidism Total- 4	STEMI (3)	-	-	-	-	-	-	1	-	1	2	-	2
	Non STE ACS (1)	-	-		-	-		-	-		-	-	
Overt Hypothyroidism Total- 1	STEMI (1)	1	-	1	-	-	-	1	-	1	-	-	-

Table 7. Lipid profile of ESS and Low FT_4 states of the study population.

Thyroid status	ACS type	High TC			High TGL			High LDL-C			Low HDL-C		
		Gender		No	Gender		No	Gender		No	Gender		No
		M	F		M	F		M	F		M	F	
ESS(16)	STEMI	5	-	6	6	-	10	3	-	4	2	1	5
	NSTE-ACS	1	-		2	2		-	1		-	2	
Low FT_4(3)	STEMI	-	1	1	-	1	1	-	1	1	1	1	2

Figure-15. Lipid profile changes in different thyroid states of the study population.

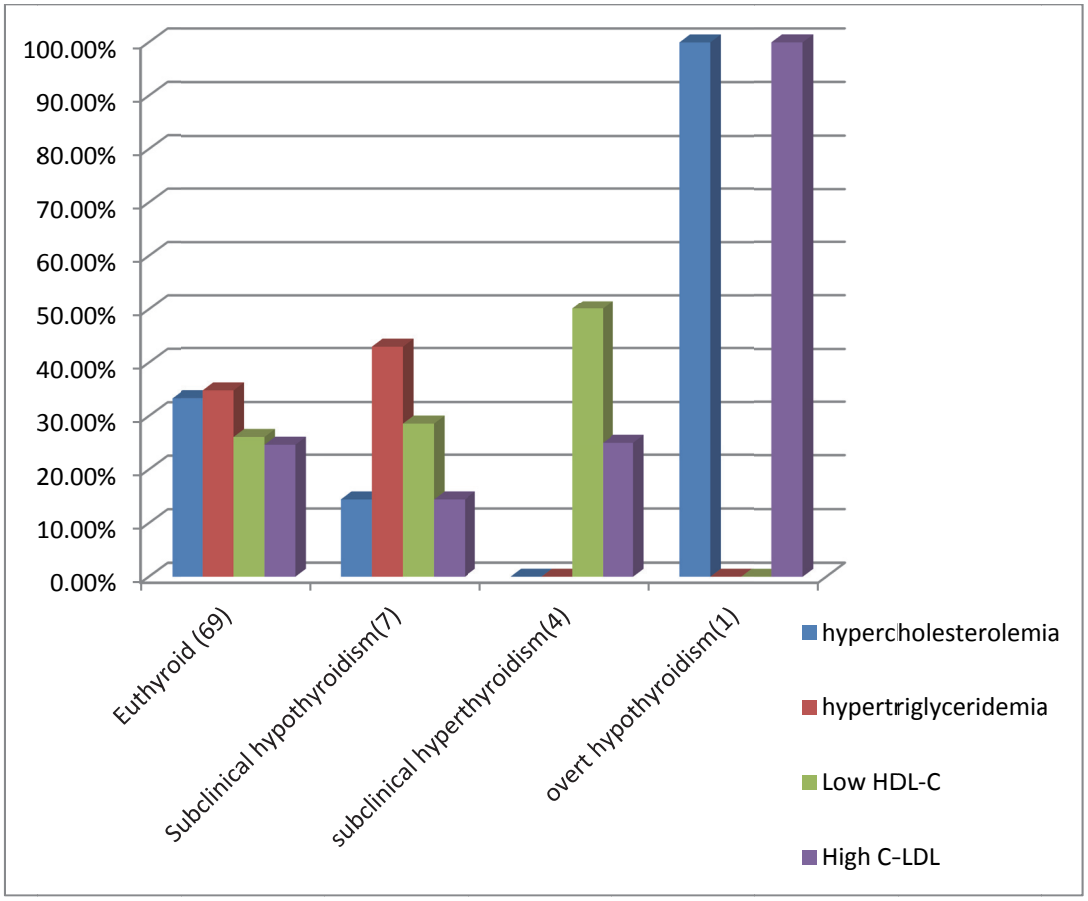
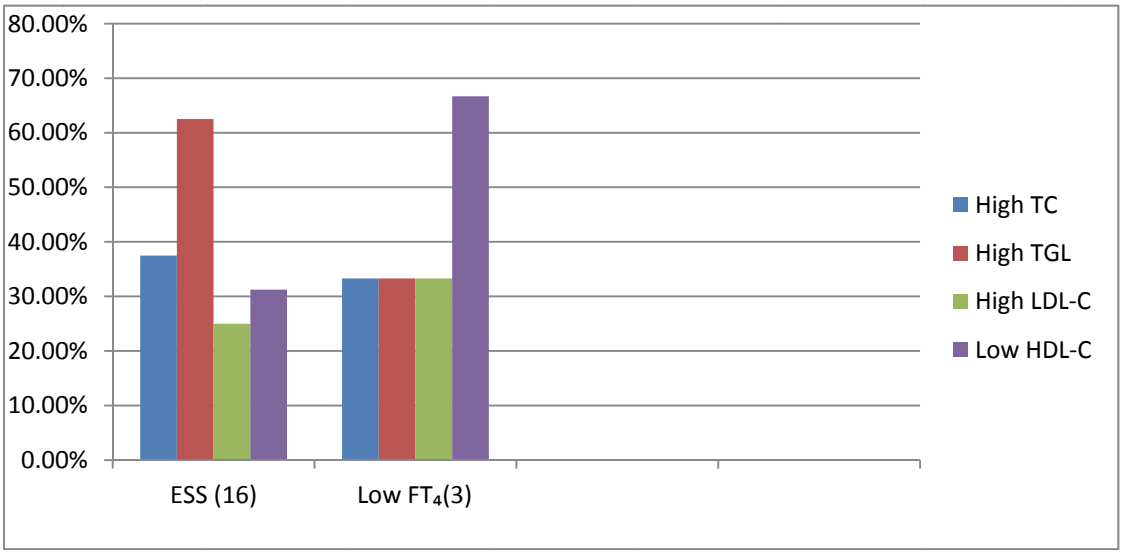


Figure 16. Lipid profile of ESS and Low FT_4 state



Thyroid status and lipid profile of the study population

Thyroid profile of Euthyroid sick syndrome was observed in 16 patients 13 of them were males. Eleven of the patients had ST elevation MI. Two of them presented with non ST elevation ACS. Out of three females, one presented with ST elevation MI and others had non ST elevation ACS. Low FT_4 was found in three patients who had presented with ST elevation MI . Two of them were females.

Analysis of numerical data

Means, standard deviations of age fasting blood glucose, urea, creatinine and CK-MB are given in Table 8.

Table. 8 Results of baseline investigations of the study population.

Variable		Number	Mean	Standard deviation
Age		100	57.05	11.15
Fasting blood Glucose		100	120.68	27.35
Urea		100	30.47	9.08
Creatinine		100	1.03	0.21
CK-MB	MI	64	247.2	197.4
	UA	36	15.5`	3.75

Data of age and fasting blood sugar was compared with serum TSH level of whole study population. There was Statistical significance. This is shown in Table 9.

Table 9. TSH vs. Age and Fasting blood glucose of ACS patients

ANALYTE	VARIABLE	NUMBER	MEAN	SD	PAIRED t TEST			
					t value	df	P value	Significance $\alpha < 0.05$
TSH	AGE	100	57.05	11.5	44	99	<0.0001	YES
	FASTING BLOOD GLUCOSE	100	120.68	27.35	42	99	<0.0001	YES

Comparisons were made between data of TSH and TC, TGL, HDL-C and Cal-LDL-C in euthyroid patients. There was significant statistical difference. Results are shown in table 10.

TABLE 10. TSH vs. LIPID PROFILE in Euthyroid patients

ANALYTE	VARIABLE	NUMBER	MEAN	SD	PAIRED t TEST			
TSH	TC	69	168.36	43.45	t value	df	P value	Significance $\alpha < 0.05$
					31.73	68	<0.001	YES
	TGL	69	142.4	76.14	15.43	68	<0.001	YES
	HDL	69	35.48	12.01	22.7	68	<0.001	YES
	Cal-LDL	69	105.02	34.06	25.1	68	<0.001	YES

Comparisons were made between data of TSH and TC, TGL, HDL-C and Cal-LDL-C in Subclinical hypothyroid patients. There was significant statistical difference. Results are shown in table 11.

Table 11.TSH vs. LIPID PROFILE in SCH patients

ANALYTE	VARIABLES	NUMBER	MEAN	SD	PAIRED T TEST			
					t value	df	P value	Significance $\alpha < 0.05$
TSH	TC	7	153.88	37.98	9.793	6	<0.0001	significant
	TGL	7	142.6	48.66	6.835	6	<0.0005	significant
	HDL	7	34.91	12.71	6.532	6	0.0006	significant
	C-LDL	7	9.99	33.74	6.01	6	0.0010	significant

Correlation studies

Pearson's correlation studies were done between data of TSH and HDL-C fraction of lipid profile in euthyroid and subclinical hypothyroid patients. There is a significant positive correlation between TSH level and HDL-C in euthyroid patients; No significant correlation was observed between TSH and HDL-C level in subclinical hypothyroid patients.

The results are shown in table 12 and 13.

Table 12.Pearson's correlation of TSH with HDL-C in Euthyroid patients

ANALYTE		TSH	HDL
TSH	Pearson correlation	1	0.28
	Sig (2 tailed)		<0.0001
	N	69	69
HDL	Pearson correlation	0.28	1
	Sig (2 tailed)	<0.0001	
	N	69	69

Table 13.Pearson's correlation of TSH vs. HDL-C in SCH

ANALYTE		TSH	HDL
TSH	Pearson correlation	1	0.3736
	Sig (2 tailed)		0.1448
	N	7	7
HDL	Pearson correlation	0.3736	1
	Sig (2 tailed)	0.1448	
	N	7	7

The TSH levels of SCH patients were correlated with Total cholesterol, Triglycerides and Cal- LDL. There was no statistically significant correlation found. XY plot for correlation study is shown in figure 17. Results are shown tables 14, 15, 16.

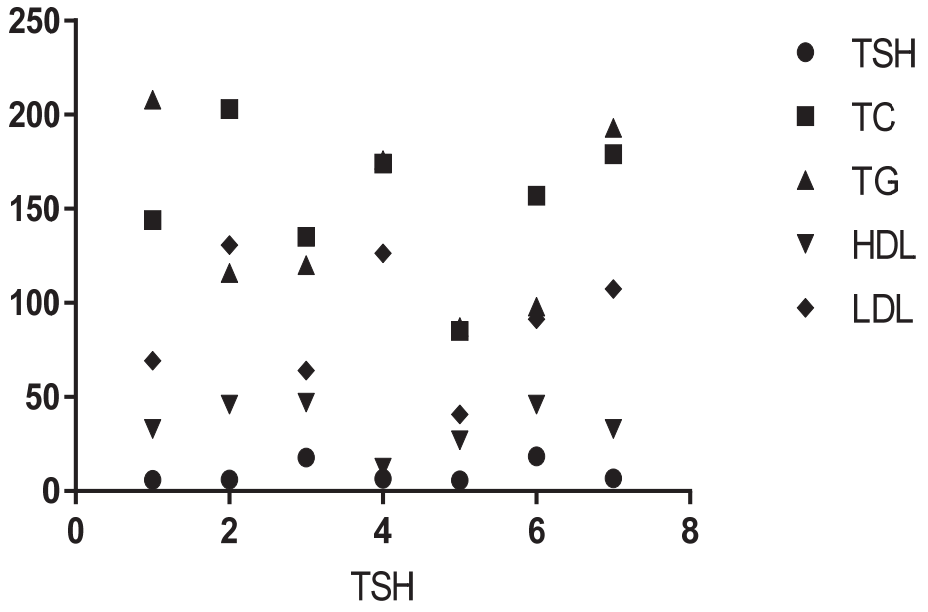


Figure17. Correlation study of TSH level with lipid profile in SCH patients

Table 14.Pearson'scorrelation of TSH with TC in SCH patients

ANALYTE		TSH	TC
TSH	Pearson correlation	1	-0.095
	Sig (2 tailed)		0.839
	N	7	7
TC	Pearson correlation	-0.095	1
	Sig (2 tailed)	0.839	
	N	7	7

Table 15.Pearson's correlation of TSH with TGL in SCH

ANALYTE		TSH	TGL
TSH	Pearson correlation	1	-0.437
	Sig (2 tailed)		0.327
	N	7	7
TGL	Pearson correlation	-0.437	1
	Sig (2 tailed)	0.327	
	N	7	7

Table16.Pearson's correlation of TSH with C- LDL in SCH

ANALYTE		TSH	C-LDL
TSH	Pearson correlation	1	-0.202
	Sig (2 tailed)		0.663
	N	7	7
C- LDL	Pearson correlation	-0.202	1
	Sig (2 tailed)	0.663	
	N	7	7

DISCUSSION

Subclinical hypothyroidism is a common form of thyroid disorder and usually asymptomatic. Most of the cases of SCH are diagnosed by screening with the support of laboratory methods. It is identified by abnormally elevated serum TSH levels with FT_4 and FT_3 concentrations within the reference range. Debate has been going on regarding the association of SCH with increased risks of altered cardio vascular hemodynamics, adverse cardiac events and lipid profile.

Lipid and Thyroid Profiles of ACS patients

On comparing thyroid status and lipid profile, our study showed that ACS patients with euthyroid profile had hypercholesterolemia in 33.3%, hypertriglyceridemia in 34%, increased LDL-C level in 24.6% and lowered HDL-C in 26.1%. Normal lipid profile at the time of presentation was observed in 31.9% of euthyroid ACS patients.

In the subclinical hypothyroid status, hypercholesterolemia occurred in 14.3% and hypertriglyceridemia in 42.9%. LDL-C level was increased in 14.3% and HDL-C level was decreased in 28.6% of SCH patients. Normal lipid profile was observed in 28.6% of SCH patients.

Results of our study revealed that patients with subclinical hypothyroidism have changes in their lipid profile only in HDL-C and triglycerides fractions rather than total cholesterol and LDL-C.

Results of our study were inconsistent with the observations of Duntas and Wartofsky study in which patients with the thyroid profile of Subclinical hypothyroidism had serum lipid profile abnormalities more in Total cholesterol and LDL-Cholesterol fractions and also with the results of Colorado study in which subclinical hypothyroid patients had more elevated serum total cholesterol concentrations than euthyroid individuals.[86] However, our results were partially concordant with NHANES III cohort study in which higher total cholesterol and triglycerides concentrations were observed in subclinical hypothyroid patients. Our study showed higher serum triglycerides concentration along with reduced HDL-C in subclinical hypothyroidism. Discrepancy between these studies may be due to the differences of the study populations, selection criteria, age, gender, race, smoking and dietary habits. Determination of normal upper limit of serum TSH concentrations to define SCH is also an important factor for these variations.

Prevalence of SCH

Our study showed that the prevalence rate of SCH was 7% among the 100 patients of ACS patients of all clinical severity. These results are in support with the study of Cooper and Biondi which reported 4% to 20% as the prevalence of SCH in adult population. This vast range could be due to differences in age, gender, race, nutritional status of the study populations, availability of Iodine in food and dietary intake of Iodine as well as methods used to do assay of serum TSH. [87]

Regarding age and prevalence of SCH, it was 4.54% in patients who were sixty years and above; 8.93% in patients who were below the age of sixty years.

Our results were not in concordance with results of NHANES III cohort study in which the prevalence increases with increasing age and also with the results of Whickham Survey [88] in which higher prevalence of SCH was observed in elderly population. But, there was no statistically significant difference in the prevalence of SCH between patients who were sixty years and above in comparison with patients who were less than sixty years.

Our results showing the prevalence 5.56% in males and 10.71% in females were also concordant with the that of the Colorado study in which the prevalence of SCH in males was 3-16% and 4-21% in females.[86] But there was no statistically significant difference in the prevalence of SCH between males and females.

Thyroid profile of Subclinical hypothyroidism was observed in 3 females. All of them were post-menopausal women. They had the TSH level of less than 10μIU/ ml.

TSH levels of two SCH patients were above10μIU/ ml. Both of them were males. Mortality was 2.9% in ACS patients (2 out of 69) with euthyroid status vs. 0% in those with SCH (p value not significant).

Other thyroid function abnormalities

Thyroid profile of ESS was found in 16 patients.14 patients were found to have low FT_3 levels. Two patients had both FT_4 and FT_3 at lower level. Three patients had low FT_4 level. These observations were concordant with studies of Vijay K S et al.[85] They found 15 ACS patients to have thyroid profile of ESS and one patient to have low FT_4 state with normal TSH and FT_3 levels.

CONCLUSION

From this study it is concluded that the prevalence of subclinical hypothyroidism in patients presented with Acute Coronary Syndrome is 7%

- 71.43% of SCH was found in ST-elevation ACS patients.
- 28.57% of SCH was found in non ST-elevation ACS patients.
- In 71.43% of SCH cases lipid profile changes were observed.

Thyroid profile of Euthyroid sick syndrome was found in 16% of whole study population.

LIMITATIONS

- The sample size of the study was small.
- In the reference range for thyroid profile, age and gender related variations were not considered.
- Variations in thyroid function tests during and after acute illness were not considered. FT_3, FT_4 and TSH were performed only once during initial hospitalization.
- Estimation of Troponin -T level was not done to diagnose ST-elevation ACS patients who present late for admission.

FUTURE PROSPECTS OF THE STUDY

Since the prevalence of subclinical hypothyroidism in patients with ACS was found to be 7% in this study and 71% of them had lipid profile changes, it can be considered as a risk factor for Coronary artery heart disease along with other risk factors. So thyroid profile can be included in any patient to assess cardio vascular risk. Large population studies are needed to confirm it.

Screening for subclinical hypothyroidism and assessment of lipid profile changes before and after treatment with levothyroxine can be done in risk groups like elderly persons, post-menopausal women, persons with family history of premature coronary artery heart disease and persons living in places where goiter is endemic.

BIBLIO GRAPHY

1 Kumar A, Sivakanesam R, G.umasekera S (2006) Ischemia modified albumin: a potential marker in acute myocardial infarction in normolipidemia. Pak J Medsci 24:364-367

2. Hallowell JG, Staehling NW, Flanders WD, Hannon WH, etal. (2009) "Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): national health and nutrition examination survey (NHANES III)," Journal of Clinical Endocrinology and Metabolism

87: 489-499.

3. Karmisholt J, Andersen S, Laurberg P (2008) "Variation in thyroid function tests in patients with stable untreated subclinical hypothyroidism," Thyroid 18: 303-308

4. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, Hansen PR, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab. 2014; **99**(7):2372–82.

5. Lloyd-Jones D, Adams RJ, and Brown TM, et al. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010; 121:948-54.

6. Mozaffarian D, Benjamin EJ, et al. Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. Circulation 2016; 133:447-54.

7. Maddox TM, Stanislawski MA, Grunewald GK, et al. Non obstructive coronary artery disease and risk of myocardial infarction. JAMA 2014; 312:1754-63.

8. Chow BJ, Small G, Yam Y, et al. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM:

COroNary computed tomography angiography evaluation For clinical outcomes: an InterRnational Multicenter registry. Circ. Cardiovasc Imaging 2011; 4:463-72.

9. Ergin A, Muntner P, Sherwin R, et al. Secular trends in cardiovascular disease mortality, incidence, and case fatality rates in adults in the United States. Am J Med 2004;117:219-27.

10. Furman MI, Dauerman HL, Goldberg RJ, et al. Twenty two year (1975 to 1997) trends in the incidence, in hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multihospital, community-wide perspective.

J Am Coll Cardiol 2001; 37:1571-80.

11. Rogers WJ, Frederick PD, Stoehr E, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008; 156:1026-34

12. Roger VL, Weston SA, Gerber Y, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction.

Circulation 2010; 121:863-9.

13. Parikh NI, Gona P, Larson MG, et al. Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart study. Circulation 2009;119:1203-10.

14. Watkins S, Thiemann D, Coresh J, et al. Fourteen-year (1987 to 2000) trends in the attack rates of, therapy for, and mortality from non-ST-elevation acute coronary syndromes in four United States communities. Am J Cardiol 2005; 96:1349-55.

15. Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease,

1987 to 1994. N Engl J Med1998; 339:861-7.m 1990 to 2006. Am Heart J 2008; 156:1026-34.

16. Joshi P, Islam S, Pais P, Reddy S, Dorairaj P, Kazmi K, Payday MR, Haque S, Mendis S, Rangarajan S, Yusuf S. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA 2007;297:286–294.

17. Cardio vascular diseases in India, current epidemiology and future directions; Dorairaj Prabhakaran; Pannyammakal Jeemon and Ambuj Roy;Ciculation,2016;133:1605-1620

18. Gupta R, Guptha S, Sharma KK, Gupta A, Deedwania P. Regional variations in cardiovascular risk factors in India: India heart watch. World J Cardiol. 2012; 4:112–120.

19. Giovino GA, Mirza SA, Samet JM, Gupta PC, Jarvis MJ, Bhala N, Peto R, Zatonski W, Hsia J, Morton J, Palipudi KM, Asma S; GATS Collaborative Group. Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. Lancet 2012; 380:668–679.

20 Lal PG, Wilson NC, Gupta PC. Attributable deaths from smoking in last 100 years in India. Curr Sci.2012; 103:1085–1090

21 Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, Prabhakaran D. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertension 2014; 32:1170–1177.

22. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365:217–223.

23. Joshi SR ,Anjana RM, Deepa M, Pradeepa R, Bhansali A, Dhandania VK, Joshi PP, Unnikrishnan R, Nirmal E, Subashini R, Madhu SV, Rao PV,

Das AK, Kaur T, Shukla DK, Mohan V; ICMR-INDIAB Collaborative Study Group. Prevalence of dyslipidemia in urban and rural India: the ICMR-INDIAB study. PLoS One. 2014; 9:e96808.

24. Wu AH, Jaffe AS. The clinical need for high-sensitivity cardiac troponin assays for acute coronary syndromes and role serial testing Am HEART j2008 Feb155 (2) 208-14

25. Goodman SG, Steg PG, Eagle KA, et al. The diagnostic and prognostic impact of the redefinition of acute myocardial infarction: lessons from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*. 2006 Mar. 151(3):654-60.

26. Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation*. 2002 Apr 16. 105(15):1760-3.

27. Miller NE. Associations of high-density lipoprotein subclasses and apolipoproteins with ischemic heart disease and coronary atherosclerosis. Am Heart J. 1987; 113:589–97.

28. Chanu B. Hypertriglyceridemia: danger for the arteries. Presse Med. 1999; 28:2011–7.

29. Abate N. Obesity and cardiovascular disease. Pathogenetic role of the metabolic syndrome and therapeutic implications. J Diabetes Complications. 2000; 14:154–74.

30. Acton SL, Kozarsky KF, Rigotti A. The HDL receptor SR-BI: a new therapeutic target for atherosclerosis? Mol Med Today. 1999; 5:518–24.

31. Yamashita S, Hirano K, Sakai N, Matsuzawa Y. Molecular biology and pathophysiological aspects of plasma cholesteryl ester transfer protein. Biochim Biophys Acta. 2000; 1529:257–75.

32. Beisiegel U. New aspects on the role of plasma lipases in lipoprotein catabolism and atherosclerosis. Atherosclerosis. 1996; 124:1–8.

33. Zambon A, Hokanson JE, Brown BG, Brunzell JD. Evidence for a new pathophysiological mechanism for coronary artery disease regression: hepatic lipase-mediated changes in LDL density. Circulation. 1999; 99:1959–64.

34. Irani K. Oxidant signaling in vascular cell growth, death and survival: a review of the roles of reactive oxygen species in smooth muscle and endothelial cell mitogenic and apoptotic signaling. Circ Res. 2000; 87:179–83.

35. Ananyeva NM, Tjurmin AV, Berliner JA, et al. Oxidized LDL mediates the release of fibroblast growth factor-1. Arterioscler Thromb Vasc Biol. 1997; 17:445–53.

36. Parola M, Bellomo G, Robino G, Barrera G, Dianzani MU. 4-Hydroxynonenal as a biological signal: molecular basis and pathophysiological implications. Antioxid Redox Signal. 1999; 1:255–84.

37. Kuhn H, Chan L. The role of 15-lipoxygenase in atherogenesis: pro- and antiatherogenic actions. Curr Opin Lipidol. 1997; 8:111–7

38. Sellmayer A, Hrboticky N, Weber PC. Lipids in vascular function. Lipids. 1999; 34(Suppl):S13–8.

39. Furchgott RF. The 1989 Ulf von Euler lecture. Studies on endothelium-dependent vasodilation and the endothelium-derived relaxing factor. Acta Physiol Scand. 1990;139:257–70.

40. Pearson JD. Normal endothelial cell function. Lupus. 2000;9:183–8.

41. Smedby O, Nilsson S, Bergstrand L. Development of femoral atherosclerosis in relation to flow disturbances.

J Biomech. 1996;29:543–7.

42. Ravensbergen J, Krijger JK, Verdaasdonk AL, Hillen B, Hoogstraten HW. The influence of the blunting of the apex on the flow in a vertebro-basilar junction model. J Biomech Eng. 1997; 119:195–205.

43. Ravensbergen J, Ravensbergen JW, Krijger JK, Hillen B, Hoogstraten HW. Localizing role of hemodynamics in atherosclerosis in several human vertebrobasilar junction geometries. Arterioscler Thromb Vasc Biol. 1998; 18:708–16.]

44. Schwedler S, Schinzel R, Vaith P, Wanner C. Inflammation and advanced glycation end products in uremia: simple coexistence, potentiation or causal relationship? Kidney Int. 2001; 59(Suppl 78):S32–6.

45. Adamopoulos S, Parissis J, Kroupis C, et al. Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Euro Heart J. 2001; 22: 791–7.

46. Kawashima S., Mitsuhiro Y. Dysfunction of Endothelial Nitric Oxide Synthase and Atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 2004; 24:998–1005.

47. Laursen J.B., Somers M., Kurz S., McCann L., Warnholtz A., Freeman B.A., Tarpey M., Fukai T., Harrison D.G. Endothelial Regulation of Vasomotion in ApoE-Deficient Mice: Implications for Interactions between Peroxynitrite and Tetrahydrobiopterin. Circulation. 2001; 103:1282–1288.

48. Griendling KK, Ushio-Fukai M. Reactive oxygen species as mediators of angiotensin II signaling. Regul Pept. 2000; 91:21–7.

49. Zalba G, Beaumont J, San Jose G, Fortuno A, Fortuno MA, Diez J. Vascular oxidant stress: molecular mechanisms and patho-physiological implications. J Physiol Biochem. 2000; 56:57–64.

50. Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesebro J. Insights into the pathogenesis of acute ischemic syndromes. Circulation.1988; 77(6):1213-1220.

51. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). N Engl J Med. 1992;326(5):310-318.

52. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation. 2001;104(3):365-372.

53. Webster MWI, Chesebro JH, Smith HC, et al. Myocardial infarction and coronary artery occlusion: a prospective 5-year angiographic study. J Am Coll Cardiol. 1990;15:218A.

54. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes: implications for plaque rupture. Circulation. 1994;90(2):775-778.

55. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994;89(1):36-44.

56. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J. 1993;69(5):377-381.

57. Sukhova GK, Schonbeck U, Rabkin E, et al. Evidence for increased collagenolysis by interstitial collagenases-1 and -3 in vulnerable human atheromatous plaques. Circulation. 1999;99(19):2503-2509.

58. Herman MP, Sukhova GK, Libby P, et al. Expression of neutrophil collagenase (matrix metalloproteinase-8) in human atheroma: a novel

collagenolytic pathway suggested by transcriptional profiling. Circulation. 2001;104(16):1899-1904.

59. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. Circulation.2000; 101(6):598-603.

60. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation.1990; 82(3) (suppl):II38-II46.

61. Lendon CL, Davies MJ, Born GV, Richardson PD. Atherosclerotic plaque caps are locally weakened when macrophages density is increased. Atherosclerosis. 1991; 87(1):87-90.

62. Tanaka A, Shimada K, Sano T, et al. Multiple plaque rupture and Creactive protein in acute myocardial infarction. J Am Coll Cardiol. 2005 May 17; 45(10):1594-1599. Epub 2005 Apr 25.

63. Sano T, Tanaka A, Namba M, et al. C-reactive protein and lesion morphology in patients with acute myocardial infarction. Circulation. 2003 Jul

64. Werner SC. Historical resume. In: IngbarSH, Breverman LE (eds) Werner's the thyroid, a fundamental and clinical text 5th edition, Philadelphia; Lippincott, 1986, p. 3-6.

65. Khatawkar AV, Awati SM. Thyroid gland historical aspects embryology anatomy and physiology. IAIM 2015 (2):165-171.

66. Decker GAG, DuPlessis DJ. Lee McGregor's Synopsis of surgical Anatomy 12th edition, Bristol; John Wright and Sons Ltd, 1986,

p. 198-205

67. Young, Barbara; et al. (2006). Wheater's functional histology: a text and color atlas (5th Ed.). Oxford: Churchill Livingstone. pp. 333–335

68. Fawcett, Don; Jensh, Ronald (2002). Bloom & Fawcett's Concise Histology. New York: Arnold Publishers. pp. 257–258.

69. Tietz text book of clinical biochemistry and molecular diagnostics 5th edition pp1907-1912.

70. Brent G. The molecular basis of thyroid hormone action. N Engl J Med.1994; 331: 847– 853.

71. Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR. Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. J Clin Invest. 2005; 115:2524 –2533.

72. Everts ME, Verhoeven FA, Bezstarosti K, Moerings EP, Hennemann G, Visser TJ, Lamers JM. Uptake of thyroid hormones in neonatal rat cardiac myocytes. Endocrinology.1996; 137:4235– 4242.

73. Lazar MA, Chin WW. Nuclear thyroid hormone receptors. J Clin Invest.1990; 86: 1777–1782.

74. Wu Y, Koenig RJ. Gene regulation by thyroid hormone. Trends Endocrinol Metab.2000; 11:207–211.

75. Danzi S, Dubon P, Klein I. Effect of serum T3 on the regulation of cardiac gene expression: role of histone acetylation. Am J Physiol Heart Circ Physiol. 2005; 289:1506-1511.

76. Hartong R, Wang N, Kurokawa R, Lazar MA, Glass CK, Apriletti, Dillmann WH. Delineation of three different thyroid hormone-response elements in promoter of rat sarcoplasmic reticulum Ca^{2+} ATPase gene.

J Biol Chem. 1994; 269:13021–13029.

77. Mintz G, Pizzarello R, Klein I. Enhanced left ventricular diastolic function in hyperthyroidism: noninvasive assessment and response to treatment. J Clin Endocrinol Metab. 1991; 73:146 –150.

78. Klemperer J, Klein I, Gomez M, Helm R, Ojamaa K, Thomas S, Isom OW, Krieger K. Thyroid hormone treatment after coronary-artery bypass surgery. N Engl J Med. 1995; 333:1522–1527.

79. Davis PJ, Davis FB. Nongenomic actions of thyroid hormone on the heart. Thyroid. 2002; 12:459–466.

80. Jin T, Teng X (2014) Update on Lipid Metabolism and Thyroid Disorders. J Endocrinol Diabetes Obes 2(3): 1043

81 Mariotti S, Franceschi C, Cosarizza A, et al. The ageing thyroid. Endocr Rev 1995; 16: 686-715.

82. Euthyroid sick syndrome A. Sattar, N. Asif, M. M. Dawood, T. Rafi, Z. Rehman*, M. Aamir JPMA (Journal Of Pakistan Medical Association) Vol. 53. No.6, June 2003

83. Subclinical Thyroid Disease: Scientific Review and Guidelines for Diagnosis and Management JAMA 2004; 291: 228-38

84. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoproteincholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18:499–502.

85. Vijay K S, Satyam P, kohli S C. Thyroid Hormone Profile in Patients with Acute Coronary Syndrome. J Endocrinol Thyroid Res. 2017; 2(4): 555592.

86. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. Arch Intern Med 160: 526-534.

87. Cooper DS, Biondi B (2012) Subclinical thyroid disease. Lancet 379: 1142-1154.

88. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, et al. (1977) The spectrum of thyroid disease in a community: the Wickham survey. Clin Endocrinol (Oxf) 7: 481-493.

ETHICAL COMMITTEE

3/17 Bio dt 3.1.17

GOVERNMENT MOHAN KUMARAMANGALAM MEDICAL COLLEGE & HOSPITAL
SALEM, TAMILNADU
College: Phone No.0427-2383313 Fax No:0427-2383193
E-Mail ID: deangmkmcslm@gmail.com
Hospital: Phone No: 0427 – 2210674, 2210757 Fax : 0427 – 2210876
E-Mail ID: msgmkmchsalem@gmail.com

Communication of Decision of the Institutional Ethics Committee(IEC)

Ref.No.GMKMCH/2623/IEC/01/2016 -32 **Dated:30.12.2016**

Protocol title	**"PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION".**
Principal Investigator	Dr. M. Mohamed Ali, I Year, Post Graduate Student of MD (Biochemistry), GMKMC, Salem.
Name of the Guide / Co - Investigator	Dr. A. LEENA DEVI, MD., Associate Professor of Biochemistry.
Name & Address of Institution	Government Mohan Kumaramangalam Medical College & Hospital, Salem, Tamil Nadu.
Type of Review	☑ New review ☐ Revised review ☐ Expedited review
Date of review (D/M/Y)	25.11.2016
Date of previous review, if revised application:	Nil
Decision of the IEC	☑ Recommended ☐ Recommended with suggestions ☐ Revision ☐ Rejected
Suggestions/ Reasons/ Remarks:	Nil
Recommended for a period of :	3 years

PLEASE NOTE:

- Inform IEC immediately in case of any Adverse events and Serious adverse events.
- Inform IEC in case of any change of study procedure, site and investigator.
- This permission is only for period mentioned above. Annual report to be submitted to IEC.
- Members of IEC have right to monitor the trial with prior intimation.

Recommended

PROFESSOR & HOD
DEPARTMENT OF BIOCHEMISTRY
GOVT.M.K.MEDICAL COLLEGE & HOSPITAL
SALEM - 636 001

Signature of Member Secretary
30/12/16
for DEAN,
Govt. Mohan Kumaramangalam
Medical College,
SALEM-636 030.

CASE PROFORMA

Date

Name Age IP NO:

Address DOA DOD

Occupation

Diet habits

Past history

Diabetes Mellitus

Hypertension

Thyroid disease

Other illness

Medication history

Smoking

Alcoholism

General examination

Pedal edema/Anemia/Clubbing /Lymphadenopathy

VITALS: BP: Pulse Rate: weight:

SYSTEMIC EXAMINATION:

CVS: Abdomen:

RS: CNS:

Investigations:

CK MB

Blood glucose fasting PP glucose

RFT Urea Creatinine

Lipid profile Total cholesterol

Triglyceride

HDL – Cholesterol

Calculated LDL

ECG Rhythm

ACS Category

Echo cardiogram

Survival

Thyroid profile

FT_3

FT_4

TSH

CONSENT

PATIENT CONSENT FORM

STUDY TITLE : PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN ACUTE CORONARY SYNDROME IN SOUTH INDIAN POPULATION

Department of Biochemistry, GMKMCH,Salem.

Participant Name : **Age/sex :**

I.P.No:

I confirm that i have understood the purpose of above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I understand that my participation in the study is voluntary and that i am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it,even if i withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

Time: signature/thumb impression of patient

Date: Patient s name:.....

Place:

Signature of the investigator .....

Name of the investigator .....

MASTER CHART

Sr No	Name	Sex	Age in Yrs	FBS	Urea	Cr	CK-MB	ACS Type	TC	TGL	HDL	Cal - LDL	FT_3	FT_4	TSH	Thyroid status
1	Kaveri	F	80	140	18	0.7	137	STEMI	142	130	37.6	78.4	2.88	1.02	3.95	EUTHYROID
2	Govindasamy	M	63	152	27	1.2	293	STEMI	86	86	22	46.8	2.8	1.23	2.87	EUTHYROID
3	Shamsavali	M	57	96	29	1.1	12	UA	83	101	14	47.8	3.05	0.88	3.00	EUTHYROID
4	Kandasamy	M	60	112	16	0.9	351	STEMI	125	59	27	86.2	1.96	0.53	3.94	LOW FT_4
5	Babu	M	48	104	26	1.2	517	STEMI	142	162	36	73.6	3.15	1.38	2.22	EUTHYROID
6	Manimegalai	65	f	160	36	1.2	69	NSTEMI	186	171	26	125.8	1.67	0.54	3.58	LOW FT_4
7	Muthu	38	m	98	38	1	12	UA	245	144	19.6	196.6	1.72	1.03	2.15	EUTHYROID
8	Madhu	42	m	113	32	0.9	18	UA	180	87	34	128.6	1.58	0.96	1.26	EUTHYROID
9	Anjalam	46	f	132	25	1.1	21	UA	186	161	33.7	128.1	2.68	0.85	1.68	EUTHYROID
10	Rajammal	70	f	106	42	1.3	512	STEMI	247	73	51.2	181.2	1.58	0.51	2.42	LOW FT_4
11	Settu	55	m	97	37	0.9	317	STEMI	210	81	51	142.8	3.09	1.74	2.40	EUTHYROID
12	Eswari	63	f	125	28	0.7	17	UA	176	117	52	100.6	2.06	0.85	1.54	EUTHYROID
13	Shahilabanu	65	f	148	36	1.2	289	STEMI	234	77	54	164.6	3.65	1.4	0.87	EUTHYROID
14	Rukmani	60	f	110	41	0.9	171	STEMI	174	176	12.4	126.4	2.67	0.81	6.50	SCH
15	Thiyagarajan	65	m	158	39	1.3	75	NSTEMI	137	80	39	82	2.21	1.5	0.21	SC- HYPER THYROIDISM
16	Natarajan	56	m	105	41	0.8	614	STEMI	121	100	16	85	2.98	1.5	1.57	EUTHYROID
17	Muthusamy	58	m	98	35	1.1	8	UA	130	94	40	71.2	2.2	1.4	3.67	EUTHYROID
18	Kangavalli	76	f	169	20	0.7	481	STEMI	153	124	33.6	94.6	1.67	1.57	0.84	EUTHYROID
19	Thangaponnu	55	f	114	36	0.8	16	UA	193	96	28.3	145.5	3.1	0.84	0.77	EUTHYROID
20	Gunasekar	58	m	108	41	1.3	13	UA	174	91	22.5	133.3	2.76	1.05	1.72	EUTHYROID

Sr No	Name	Sex	Age in Yrs	FBS	Urea	Cr	CK-MB	ACS Type	TC	TGL	HDL	Cal - LDL	FT_3	FT_4	TSH	Thyroid status
21	Chellammal	70	f	136	28	1	267	STEMI	108	83	27	64.4	1.14	1.55	1.47	ESS
22	Dhanalakshmi	47	f	143	37	1.2	19	UA	134	123	39.4	70	1.56	0.84	1.32	EUTHYROID
23	Manivel	53	m	103	31	1	22	UA	159	154	42.5	85.7	2.3	0.92	0.78	EUTHYROID
24	Alamelu	62	f	136	25	1.2	294	STEMI	147	153	44	72.4	1.74	0.9	1.17	EUTHYROID
25	Kalaimani	54	f	112	33	0.8	16	UA	147	173	36.4	76	2.26	1.24	1.16	EUTHYROID
26	Manikandan	38	m	152	23	0.9	198	STEMI	229	356	31.3	126	1.58	0.91	1.16	EUTHYROID
27	Mariappan	73	m	102	42	1.3	834	STEMI	173	145	19.1	124.9	2.7	1.08	1.11	EUTHYROID
28	Thangavel	70	m	162	39	1.1	475	STEMI	180	543	33.1	38.3	1.02	0.87	1.38	ESS
29	Andiappan	62	m	97	16	0.8	13	UA	147	153	44	72.4	0.04	0.97	1.17	ESS
30	David	63	m	93	21	0.8	392	STEMI	240	122	46	169	0.52	1.41	0.51	ESS
31	Veeramuthu	70	m	132	34	1.3	16	UA	208	273	56	117.8	0.56	0.97	3.65	ESS
32	Saravanan	49	m	113	27	1.1	109	STEMI	140	186	39.3	63.5	0.05	0.61	0.66	ESS
33	Mariammal	58	f	153	42	1.1	75	STEMI	139	102	37	81.6	1.86	0.96	1.26	EUTHYROID
34	Muthukumar	52	m	170	16	0.8	83	STEMI	189	193	40.7	109.7	2.09	0.82	3.99	EUTHYROID
35	Gnanasekar	60	m	192	27	1.4	16	UA	90	120	21.8	44.2	2.27	1.17	2.12	EUTHYROID
36	Shanawaz	52	m	181	15	1	115	STEMI	188	139	46.9	113.3	1.12	1.04	0.61	ESS
37	Irusappan	65	m	97	17	1.2	153	STEMI	219	94	38.4	161.8	1.83	0.88	1.42	EUTHYROID
38	Amutha	40	f	117	26	0.9	11	UA	175	158	29.8	113.6	1.56	0.85	2.58	EUTHYROID
39	Valli	53	f	94	32	1.2	14	UA	136	118	42	75.8	2.4	1.24	2.67	EUTHYROID
40	Murugesan	46	m	107	37	1.3	20	UA	156	138	23.6	95.8	1.7	1.46	0.94	EUTHYROID
41	Gopal	60	m	102	36	1	236	STEMI	237	181	51	149.8	2.03	0.91	1.52	EUTHYROID
42	Lakshmi	70	f	97	41	1.3	19	UA	145	264	16.6	75.6	1.12	0.55	2.05	ESS
43	Rathinam	58	m	98	23	1.1	9	UA	164	333	33	64.4	1.87	1.03	1.25	EUTHYROID
44	Gandhi	67	m	89	43	0.9	176	STEMI	137	139	16	93.2	3.35	0.95	1.38	EUTHYROID
45	Sundaram	65	m	119	57	0.9	27	STEMI	147	171	28	84.8	1.05	0.61	0.85	ESS

Sr No	Name	Sex	Age in Yrs	FBS	Urea	Cr	CK-MB	ACS Type	TC	TGL	HDL	Cal - LDL	FT_3	FT_4	TSH	Thyroid status
46	Mariammal	56	f	104	41	1.2	17	UA	143	123	29.6	88.8	1.42	1.37	2.16	EUTHYROID
47	Subramanian.A	45	m	145	18	0.8	97	STEMI	171	151	54	86.8	1.44	1.03	0.52	EUTHYROID
48	Velu	63	m	86	32	0.8	489	STEMI	225	138	43	154.4	1.07	0.9	0.61	ESS
49	Palanisamy.A	50	m	97	20	0.8	67	STEMI	169	127	12.4	132.2	1.64	0.94	0.12	SC-Hyper Thyroid
50	Kasinathapillai	95	m	105	24	0.6	398	STEMI	161	58	38	111.4	1.89	0.83	2.02	EUTHYROID
51	Ratjathi	58	f	127	18	0.6	834	STEMI	149	139	30	91.2	1.57	1.45	0.76	EUTHYROID
52	Rajamanckam	74	m	115	32	0.9	16	UA	151	90	32	100	1.66	1.08	2.21	EUTHYROID
53	Subramanian.A	70	m	139	18	0.8	283	STEMI	162	77	37	130.8	4.13	1.78	1.06	EUTHYROID
54	Mani	62	m	195	29	1.1	106	STEMI	145	92	34	91.6	1.6	1.22	3.04	EUTHYROID
55	Ayyappan	65	m	106	32	1.2	65	STEMI	203	116	46	130.8	1.78	1.25	6.08	SCH
56	Palanisamy	66	m	113	36	1.3	74	STEMI	142	103	36	91.4	1.87	1.36	2.78	EUTHYROID
57	Mansoor	45	m	93	27	1.1	11	UA	136	117	42	78.6	1.54	0.95	0.54	EUTHYROID
58	Rathinam	60	m	105	25	0.9	105	STEMI	209	180	47	126	1.55	1.101	0.51	EUTHYROID
59	Kandasamy.S	80	m	132	31	0.9	94	STEMI	131	59	35	84.2	1.81	0.92	0.27	SC-Hyper Thyroid
60	Periyasamy.A	46	m	88	30	1.1	12	UA	157	98	46	91.4	1.57	0.98	18.36	SCH
61	Vaithyanathan	34	m	106	17	0.8	158	STEMI	190	428	33	71.4	1.59	0.86	2.30	EUTHYROID
62	Zakariya	65	m	98	36	1.2	115	STEMI	197	173	32.8	129.6	2.33	0.96	4.83	EUTHYROID
63	Perumal	59	m	124	31	1.3	119	STEMI	130	77	48.6	66	1.13	1.45	0.60	ESS
64	Duraisamy	70	m	101	24	0.7	177	STEMI	170	140	32	110	4.28	1.7	2.68	EUTHYROID
65	Chinnammal	38	f	152	43	1.2	19	UA	255	212	28	184.6	1.01	1.28	0.73	ESS

Sr No	Name	Sex	Age in Yrs	FBS	Urea	Cr	CK-MB	ACS Type	TC	TGL	HDL	Cal - LDL	FT_3	FT_4	TSH	Thyroid status
66	Chitra	55	f	160	45	0.9	75	STEMI	85	87.2	26.9	40.66	3.08	1.21	5.63	SCH
67	Shajahan	52	m	111	37	0.8	110	STEMI	90	120	21.8	44.2	2.27	1.17	2.12	EUTHYROID
68	Mahesh	34	m	97	23	0.9	588	STEMI	198	202	15.6	142	3.76	0.88	2.56	EUTHYROID
69	Syed	65	m	89	33	1.2	158	STEMI	107	138	26.4	53	3.25	1.17	1.98	EUTHYROID
70	Chandhran	63	m	113	42	1.1	280	STEMI	166	94	32.8	114.4	4.02	0.95	0.98	EUTHYROI
71	Shunmugam	63	m	121	41	1.2	105	STEM	209	101	51.6	137.2	2.19	0.96	4.24	EUTHYROID
72	Padhmavathy	47	m	165	34	1.4	21	UA	179	193	33	107.4	1.51	1.28	6.78	SCH
73	Premnath	37	f	87	19	1	130	STEMI	357	493	94	164.4	1.46	0.89	1.03	EUTHYROID
74	Chinnasamy.S	44	m	102	15	1	86	STEMI	159	86	44	97.8	0.07	0.83	0.90	ESS
75	Subramanian	58	m	98	36	1.3	17	UA	184	69	41.9	128.3	1.96	1.47	3.17	EUTHYROID
76	Rathinasamy	67	m	116	33	1.1	12	UA	118	93	27	72.4	1.75	1.45	2.47	EUTHYROID
77	Samiyannan	50	m	156	19	0.6	834	STEMI	135	120	47	64	2.4	0.87	17.88	SCH
78	Manoharan	52	m	98	45	1.2	280	STEMI	148	62	10.6	125	3.09	0.92	0.29	SC-Hyper Thyroid
79	Soundara rajan	65	m	115	35	1.2	19	UA	167	123	36.4	106	1.81	1.16	1.18	EUTHYROID
80	Pappa	75	m	131	39	1.3	11	UA	223	156	31.3	160.5	1.41	0.82	3.75	EUTHYROID
81	Velsamy	70	f	116	18	0.9	293	STEMI	207	81	51	139.8	3.56	1.2	3.60	EUTHYROID
82	Murugesan	54	m	92	27	1	398	STEMI	241	122	38	178.6	1.19	0.43	33.32	OVERT - Hypothyroid
83	Selvam	54	m	154	24	0.9	177	STEMI	322	211	10	269.8	1.11	0.69	0.56	ESS
84	Rukmani	56	m	117	31	1.3	10	UA	154	108	33.1	99.3	2.23	1.68	3.60	EUTHYROID
85	Kurshidh banu	55	f	89	36	1.1	17	UA	132	98.8	44.2	68.04	1.84	1.17	2.15	EUTHYROID

Sr No	Name	Sex	Age in Yrs	FBS	Urea	Cr	CK-MB	ACS Type	TC	TGL	HDL	Cal - LDL	FT_3	FT_4	TSH	Thyroid status
86	Sankar	49	f	117	32	1.2	13	UA	149	151	43.9	82.7	1.9	1.04	0.81	EUTHYROID
87	Rangasamy	38	m	99	29	0.9	293	STEMI	134	183	29.6	67.8	1.67	1.47	3.06	EUTHYROID
88	Chinnathamby	60	m	96	26	1	485	STEMI	174	59	41.9	120.3	2	1.57	1.17	EUTHYROID
89	Prakash	32	m	128	18	0.8	283	STEMI	144	208	33.1	69.3	3.1	1.79	6.04	SCH
90	Sivagnanam	46	m	212	17	0.9	142	STEMI	272	755	44	77	1.08	0.08	0.65	ESS
91	Ravi	61	m	127	38	1.1	19	UA	216	155	44	141	1.62	0.85	0.79	EUTHYROID
92	Maniammal	48	m	118	32	0.8	21	UA	137	133	34	76.4	1.59	1.35	1.19	EUTHYROID
93	Periyasamy	55	f	156	41	1.4	156	STEMI	127	100	41	66	0.9	1.14	0.56	ESS
94	Govindan	41	m	75	15	0.7	114	STEMI	223	249	32	141.2	3.9	1.75	0.96	EUTHYROID
95	Karuppannan	57	m	106	42	0.9	91	NSTEMI	177	125	19.1	132.9	2.58	1.01	1.32	EUTHYROID
96	Santhana lakshmi	62	m	123	46	1.5	15	UA	182	153	33.1	120.3	1.41	0.87	1.89	EUTHYROID
97	Mani.s	61	f	98	37	1.3	16	UA	158	113	35	100.4	1.53	0.97	2.23	EUTHYROID
98	Srinivasan	42	m	162	26	1.2	155	STEMI	116	149	41.5	44.7	2.89	0.83	0.71	EUTHYROID
99	Raju	41	m	114	23	1.1	313	STEMI	223	197	27.3	160.3	4.14	0.85	0.67	EUTHYROID
100	Krishnammal	58	f	137	18	0.9	588	STEMI	125	167	25.1	70.1	3.48	1.12	2.56	EUTHYROID